POSTMARKETING SURVEILLANCE OF PROTON PUMP INHIBITORS IN PERSPECTIVE

THE CASE OF LANSOPRAZOLE

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POSTMARKETING SURVEILLANCE OF PROTON PUMP INHIBITORS IN PERSPECTIVE

THE CASE OF LANSOPRAZOLE

POSTMARKETING SURVEILLANCE VAN PROTONPOMPREMMERS IN PERSPECTIEF

EEN VOORBEELD MET LANSOPRAZOL

(Met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1

Scope of the thesis

INTRODUCTION

There is a continuous need to monitor and evaluate the effectiveness and safety of medicines when they are used in daily clinical practice after their release for marketing [1, 2]. Safety is a key issue in the appraisal of drug therapy outcomes [3-5]. Drug related problems are probably one of the most frequently occurring and significant health hazards [6].

Recently, the withdrawal of five drugs from the US market in a 12-month period has raised concerns about the role of pre- and postmarketing regulations with respect to drug safety. Friedman et al have reviewed these cases and came to the conclusion that the approval dates of these removed drugs were scattered over the last decades, making a time association between the recently established reduction of review time at the FDA and the drug withdrawals not very likely [3]. Balancing the risks and benefits of drug treatment is one of the most challenging responsibilities of all stakeholders in pharma (prescribers, industry, pharmacists, regulators, academia) [4, 5].

The effectiveness, safety, and patterns of use of a drug in real life may be different than as assessed in clinical trials due to differences in prescribing physicians and patients. Key differences between clinical trials and the 'real world' are the limited patient numbers, restrictions in the patient populations (e.g. pregnant women, children, elderly and those predisposed to develop adverse events are frequently excluded) and the limited duration of drug use in clinical studies [4]. Effectiveness and safety when used for indications or in dosages other than initially tested remain unknown and knowledge about interactions with concomitantly used drugs due to multiple pathology is not always complete. Moreover, physicians' prescribing habits are often unknown at the time of market entry and may vary over time due to commercial promotion, cost containment measures, changing attitudes and guidelines of therapeutic evidence [7].

Postmarketing surveillance aims to monitor and evaluate both the beneficial and adverse effects of drugs after approval for general use. The Health Council in the Netherlands has defined postmarketing surveillance (PMS) as 'The systematic surveillance and scientific study of all intended and unintended effects of medicines on human health, after their release for marketing' [8]. Spontaneous reporting systems have been shown to be effective in revealing unusual or rare ad-

verse events [4]. However, spontaneous reports alone do not provide sufficient evidence to conclude that an adverse event is indeed drug related. Recently, McNeil et al demonstrated the limitations of spontaneous reporting in relation to the antibiotic agent flucloxacillin [9]. There were such reports from Australia, New Zealand and UK suggesting flucloxacillin-associated jaundice, but these data were insufficient to test the hypothesis of a causal association. Spontaneous reports should be supplemented by analytical studies, monitoring of cohorts of users of new drugs, using record-linkage to track their subsequent outcomes, and to interpret the results of such analyses in the context of variability of drug exposure [7].

Several designs can be applied to investigate medicines after approval for marketing, either descriptive or analytical, and either non-experimental or experimental [2, 10-14].

Record-linkage has made a significant contribution to postmarketing surveillance of drugs, which involves linking drug exposure to outcome data (effectiveness, safety, economics) [10-12]. Even patient reporting can play an important role in pharmacovigilance, as reporting by patients may lead to earlier notice of adverse events [15].

There are many significant features of drug exposure and related outcomes to be studied in postmarketing surveillance, such as time dosing of medicines in daily use, prescription patterns, dynamics of indications and off-label use.

Examples of such topics in postmarketing evaluation of medicines include also fine-tuning of dosage recommendations, a reappraisal of indications (extension or restriction), drug use and drug users characteristics, assessment of long-term efficacy, assessment of side effects detection of unexpected side effects and interactions, long-term safety, study of potential risk groups, detection of unexpected beneficial effects, further pharmacological and mechanistic studies, and finally cost-effectiveness studies [2, 7].

Illustrations of such approaches comprise a postmarketing study regarding the teratogenetic metabolite of acitretin [16]. Furthermore, the introduction of drugs with a new pharmacological profile especially requires postmarketing surveillance of adverse events, as illustrated by the case of ibopamine [14].

Automated databases and field cohort studies in postmarketing surveillance

One of the most productive approaches in postmarketing surveillance has been the use of automated databases including ample data on drug exposure, clinical characteristics of patients and health outcomes. The European scene of the automated databases is fairly straightforward [2]. In The Netherlands, Herings et al have developed the PHARMO Record Linkage System, in the United Kingdom GPRD and MEMO are widely recognised as valuable sources for postmarketing studies, in Odense (Denmark) the so-called OPED database has been shown to be an important asset and in Italy the county of Friuli has developed a relevant database for pharmacoepidemiologic work [2, 10, 12]. In North-America (including Canada) there is ample opportunity to approach automated databases for postmarketing surveillance (e.g. large number of HMOs, Saskatchewan, Medicaid) [2]. However, automated databases frequently have important limitations regarding reliability and completeness of records on baseline health and disease status, longitudinal clinical data (e.g. course of disease, data on hypertension, cholesterol level) and health behaviour (smoking, drinking, OTC drugs) [4, 17]. In case of postmarketing surveillance of a newly launched drug, there are three other reasons why automated databases may be not the first choice for conducting postmarketing surveillance studies:

1. Selection: Adoption of a new drug by physicians is highly variable and often unpredictable due to differences in prescribing attitudes, formulary policies, and marketing practices.
2. Size: In general, the introduction of a new drug on the Dutch market hardly ever leads to a population of first users exceeding the size of 15-20,000 in the first year after marketing. Currently PHARMO for instance, covers around 2% of the Dutch population and thus can only provide information on a group of between 300 and 400 patients in the first year.
3. Access: Many databases have a lag time between data recording and availability for research (although advances in IT have led to significant improvements here).

Thus, the limitations of automated databases and the specific features of new drug prescribing have fostered the development of alternative strategies for building field cohorts of recipients of a new drug and performing follow-up monitoring and evaluation [17].

Since the early days of such field cohort studies in the late 80s, concerns have been expressed about industry bias, seeding pressure in the form of pushing prescriptions, and ethical issues related to industry sponsored postmarketing cohort studies [18-21]. Discussions began regarding whether studies performed with marketed drugs, where the physicians get paid for their participation, were scientifically justified or were simply to increase sales [22].

One of the first 'whistleblowers' here was Inman. He blamed industry for the promotional nature of their postmarketing surveillance studies and expressed concerns about the consequences of physicians' participation in such studies with respect to the response rate to contribute to the prescription-event monitoring (PEM) system organised by the Drug Safety Research Unit in UK [18]. Inman found that general practitioners (GPs) heavily involved in promotional postmarketing studies were frequent prescribers of the drugs under investigation in such studies. There was a consistent inverse relation between the number of prescriptions per individual GP and the response rate to PEM. The overall response among GPs was 53%, but the heaviest 10% of prescribers returned only 44% and the heaviest 1% returned only 34% of PEM questionnaires.

Waller et al published an important analysis on industry sponsored postmarketing studies in 1992 [23]. They concluded that such studies, because of weak study design and problems with recruitment, had made only a limited contribution to the assessment of drug safety to date. Based on the recommendations of Waller et al several attempts have been made to design better and scientifically more rigorous postmarketing surveillance models. This development has led to the establishment of European guidelines for Safety Assessment of Marketed Medicines (SAMM) [24]. These guidelines were developed in draft form in 1993 by a joint committee with members with a clinical, regulatory, academic or pharmaceutical industry background in order to provide basic rules to ensure good study design. A legal framework is given in Council Regulation (EEC) No 2309/93 (Title 2, Chapter III) and Council Directive 75/319/EEC as amended (Chapter Va) [25]. The obligations apply to all authorised medicinal products, are clarified in the draft-Notice to Marketing Authorisation Holders and incorporate among other things that the design of company sponsored postmarketing surveillance studies will depend on the objectives of the study, which must be clearly defined in the study protocol. Specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods. Although the

SAMM guidelines cover different designs of studies (observational cohort studies, case-control studies, case-surveillance and clinical trials) they have mainly been used for the conduct of cohort studies [26, 27].

At present, several European countries have published guidelines for the conduct of postmarketing studies in accordance with the above-mentioned guidance of the European Union. Promotional activities conducted under the guise of postmarketing studies remain unacceptable. The field of such studies shows a continuous process of 'trial and error' of finding the right balance between scientific work, involvement of health practitioners and patients and promotional activities. Although the SAMM guidelines provide a useful format for finding the right balance, postmarketing practice has shown several cases of studies leading to debate and critique. Ayres et al have reported from a postmarketing surveillance study to evaluate the safety of a non-chlorofluorocarbon metered dose salbutamol inhaler [28]. This study was conducted according to the SAMM-guidelines and was a comparison of safety in patients using prescribed metered doses of salbutamol delivered by inhalers using either hydrofluoroalkane or chlorofluorocarbon as the propellant. There were no significant differences in hospitalisations and reports of adverse effects between the hydrofluoroalkane and chlorofluorocarbon inhaler groups. Although the study design successfully fulfilled the recommendations of the SAMM guidelines, several authors have criticised the study for being to promotional, and for being unethical [29, 30].

On the other hand one sees an increasing visibility of industry in types of postmarketing surveillance studies resulting in clinically relevant findings [31, 32]. Although general maturity is not yet established, there is an increasing awareness among industry pharmacovigilance and pharmacoepidemiology professionals to continue in challenging their marketing colleagues to improve standards within the industry. Moreover, academic pharmacoepidemiology has increased its contribution significantly to drug safety studies and is now representing a strong partner in solving important drug risk questions [33, 34].

PERSPECTIVE OF THE STUDY

With this background of interest in postmarketing research and the recognised additional value of results of postmarketing surveillance studies, Aventis Pharma B.V. and Janssen-Cilag B.V. took the initiative to set up the Peptic Survey proj-

ect. Peptic Survey was a postmarketing surveillance study with lansoprazole, the second proton pump inhibitor (PPI) introduced on the Dutch market at the end of 1993 by the previously mentioned pharmaceutical companies [35]. At the time of product launch, the drug was indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers. The drug was introduced at first as a 30 mg capsule, while in January 1996 a 15 mg capsule was launched for the same indications. At the time of introduction, lansoprazole had been evaluated in several thousands of patients enrolled in clinical trials. The widespread use of PPIs justified a thorough assessment of the safety of these drugs. The study started soon after the introduction of lansoprazole on the Dutch market. All objectives were clearly defined in the study protocol and/or amendments of the protocol.

Objectives

The primary objectives of this study were to assess the safety and effectiveness of lansoprazole in a population composed of naturally occurring groups of users and to evaluate the patterns of use of lansoprazole in daily practice. Secondary objectives were to identify factors related to non-reponse to lansoprazole, headache or diarrhoea during lansoprazole use and to evaluate the use of lansoprazole as part of a *Helicobacter pylori (H. pylori)* eradication therapy.

Design

The study was a prospective, open label, observational follow-up study carried out in naturally occurring users of lansoprazole in the Netherlands. The total duration was aimed to be at least two years, and in fact was extended to 4 years and 3 months. The study protocol was designed in the fall of 1993, whereas European guidelines for the design of company sponsored postmarketing surveillance studies at first became available in December 1993.

Nevertheless, the design incorporated five of the six recommendations of the European SAMM guidelines, namely:

1. A population as representative as possible of the general population of users, and not selected. No in- or exclusion criteria were considered;
2. The medicinal product must be prescribed in the usual manner;
3. Patients must not be prescribed the medicine in order to include them;

4. The decision to prescribe must be clearly separated from the decision to include the patient in the study;
5. The protocol stipulated the maximum number of patients to be entered by a single physician [24].

The recommendation to include an appropriate comparator group was not followed. This was due to two reasons; firstly, at the time of initiation of our study only one other PPI was available on the Dutch market, which limited our choice. Secondly, for reasons of efficiency we chose to make use of internal comparisons in the analyses. As advised in the guidelines an independent scientific advisory group was appointed to monitor the data and to oversee the study.

For day-to-day management a project team was installed. This team consisted of an independent chairman, a project leader of Aventis Pharma B.V., a member of Janssen-Cilag B.V. (during the first phase) and a member of the independent Contract Research Organisation Kendle. The Medical Ethical Committee of the Utrecht University Medical Centre approved the protocol. The highest standards of professional conduct and confidentiality were maintained throughout the study. All data and documents were kept in strict confidence and in accordance with the privacy regulations.

Study population

All GPs, internists and gastro-enterologists in The Netherlands were invited to participate in the study (Appendix I). In order to avoid inclusion bias, participating physicians and pharmacists were remunerated with only a modest fee, equivalent to the reimbursement of their time spent to complete the record forms or generate the medication histories. GPs could include a maximum of 20 patients per two years follow-up time, while specialists were allowed to include not more than 50 patients in the same period. It was estimated that 5,000 to 10,000 patients, to whom lansoprazole was prescribed in daily practice, might participate in this study following the recommendations available at that time. All procedures of patient inclusion, data recording and monitoring were designed not to influence normal prescribing practice. Lansoprazole was prescribed without any form of intervention or randomization. The patients' pharmacist, as part of routine pharmaceutical care, provided the medicines.

All patients having used, or using lansoprazole, could be included in the study at the first visit or any later follow-up visit after lansoprazole was prescribed. The decision to prescribe was therefore clearly separated from the decision to include the patient in the study. Furthermore, patients could not be prescribed the medicine in order to include them, but must be natural occurring lansoprazole users. Patients were informed about the project and agreed to participate by giving their written informed consent to allow access to all relevant clinical and medication data and storage and analyses of these data (Appendix II). No further selection criteria were considered. All lansoprazole users could be included independent of for example, age, indication for use, co-morbidity, and use of co-medication. To maintain patient anonymity patients were identified by an identification code only. All data and documents related to patients included were kept in strict confidence and in accordance with Dutch privacy regulations.

Data were collected at the inclusion visit and at follow-up visits during lansoprazole therapy by reviewing the medical file and by patient questionnaire. Data collection was designed not to influence daily practice. No supplementary diagnostic tests were requested from the physician with regard to the indication. Complete medication histories were constituted through pharmacy records six months retrospectively and during the lansoprazole therapy. Computerization of pharmacy records, and thus the compilation of medication histories, is almost universal in the Netherlands. The majority of patients are designated to a single pharmacy for all reimbursed prescription drugs. In our study, the physician requested the appropriate pharmacy to collect the pharmacy records.

For a subset of patients included after December 31st 1995 additional evaluation forms regarding headache, diarrhoea and/or lack of effectiveness were completed by the physician and, where applicable, after consultation with the patient in question. In addition, for all patients during the total study period where lansoprazole was used as part of a *H. pylori* eradication therapy, additional evaluation forms were completed by the physician.

To ensure the collection of accurate, consistent, complete and reliable data participating physicians were instructed and monitored in completing the forms at regular intervals by representatives of the pharmaceutical companies and/or the independent Contract Research Organisation.

All data collected by the participating physicians and pharmacists were entered in databases, validated and analysed by the independent Contract Research Organisation in conjunction with the Department of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences (UIPS). Inquiries were made in case of inconsistencies, incorrect data, and missing data. The decision to communicate or to publish depended upon the scientific merit and interest in the findings and was agreed by the independent scientific advisory group. The authors of all publications were not associated with the sponsors of the study.

During the first two years data of 5,669 patients were analysed, resulting in two chapters of the thesis (Chapters 2.1 and 4.2). The second two years another 4,339 patients were included. The total number of 10,008 patients comprised the source of all other chapters.

OUTLINE OF THE THESIS

In Chapter 2 of the thesis the general response to PPI therapy of the project Peptic Survey is given. The design of the study is described in detail and the results of the primary objectives regarding safety, effectiveness and patterns of use are captured in Chapter 2.1. Since PPIs have a high efficacy, we were interested to identify possible co-factors associated with lack of effectiveness during lansoprazole use (such as compliance, diagnosis and acid-relatedness of complaints). For this reason we compared patients with lack of effectiveness on treatment (‘non-responders’) versus control patients without lack of effectiveness on treatment (‘responders’) in Chapter 2.2.

In Chapter 3 drivers of PPI treatment were the key elements of our investigation. In Chapter 3.1 we investigated the increasing amount of combined prescriptions of NSAIDs and PPIs. We assessed how frequently PPIs were prescribed in combination with NSAIDs in order to prevent acid related disorders and to treat NSAID induced acid related disorders. In Chapter 3.2 we investigated whether the study has led to selection bias regarding inclusion of patients in the study and whether the design of this study was susceptible to driving prescriptions.

The role of *H. pylori* and the role of PPIs in the eradication of *H. pylori* have become very important in the last years. In addition to existing results of clinical

trials, a study was set up to investigate the characteristics and the effect of time of *H. pylori* eradication therapy in daily clinical practice of lansoprazole users. This research is captured in Chapter 4.1.

Therapies combining antibiotics and PPIs, including dual, triple and quadruple schedules have been shown to be effective in clinical trials to eradicate *H. pylori* in peptic ulcer patients, whether this results in improved symptoms in clinical practice remains unclear. In Chapter 4.2, we investigated continued use of lansoprazole treatment after *H. pylori* eradication therapy and evaluated possibly related determinants of such continuation in daily clinical practice.

In Chapter 5, the safety of lansoprazole in 10,008 users was assessed. Frequencies and incidence densities were calculated for all adverse events and the pattern in time was given, as can be read in Chapter 5.1. In addition, two subsets were used to investigate two frequently reported adverse events during lansoprazole use, namely headache and diarrhoea. Besides the high prevalence, these adverse events often lead to a discontinuation of a PPI. These subsets were used to investigate the frequency and characteristics of the adverse event during lansoprazole use and to possibly find relevant co-factors associated with the occurrence of the adverse event by comparing patients with the occurrence of the adverse event to those without. These results are given in Chapter 5.2 and 5.3.

Chapter 6 gives a summary of the findings and a discussion of the implications of our results.

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Chapter 2

Response to proton pump inhibitor therapy

Chapter 2.1

A prospective follow-up study in 5,669 users of lansoprazole in daily practice

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SUMMARY

Background: Right after the introduction of the proton pump inhibitor (PPI) lansoprazole (Prezal®) a 2-years follow-up study was started to evaluate patterns of use, safety and effectiveness of this drug in naturally occurring groups of patients in the Netherlands. Medical data were recorded by participating physicians while medication listings were provided by pharmacists.
Methods: The study was designed according to the SAMM guidelines. The only inclusion criterion was the use of lansoprazole prior to entry into the study.
Results: A total of 5,669 lansoprazole users were included by 374 general practitioners (GPs) and 117 specialists. Lansoprazole was mostly prescribed in patients with reflux oesophagitis (55.1%), 'gastritis' (26.8%) and duodenal ulcers (11.4%), sometimes as part of *Helicobacter pylori (H. pylori)* eradication therapy (8.5%). For their complaints most patients (91.1%) had previously used acid-related drugs. Improvement or disappearance of complaints was achieved in 88.9% and 90.5% of patients after 4 and 8 weeks of treatment, respectively. Diarrhoea (4.1%), headache (2.9%) and nausea (2.6%) were the most frequently reported adverse events.
Conclusion: The patterns of use of lansoprazole in daily practice deviated from the recommendations in the information leaflet. Nevertheless, lansoprazole was found to be safe in this naturally occurring group of users. Effectiveness appeared to be comparable to results found in clinical trials in the registered indications for lansoprazole.

INTRODUCTION

Healing of peptic lesions can be achieved by using a variety of medications. The most commonly used agents are the H_2- receptor antagonists and the newer PPIs. Lansoprazole (Prezal®) is a new PPI which produces prolonged decrease of gastric acidity [1, 2]. The drug has been introduced on the Dutch market at the end of 1993 as a 30 mg capsule indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers.

At the time of introduction, lansoprazole had been evaluated in several thousands of patients enrolled in clinical trials. These trials showed that the drug is highly effective in healing of duodenal ulcers (94-98% at week 4), gastric ulcers (87-96% at week 8) and reflux oesophagitis (85-88% at week 4) when administered at therapeutic dosages [1, 3-5].

Lansoprazole provides effective symptom relief in those patients of 90-100% at week 4 [1]. Healing rates in those patients are much higher compared to rates in patients using H_2-receptor antagonists [2, 3, 6-8]. In addition, healing rates of gastric ulcers, duodenal ulcers and reflux oesophagitis with lansoprazole 30 mg were equivalent or better compared to healing rates of omeprazole, the first PPI that was available, in a dose of 20 mg [4, 9-11]. Treatment of patients with reflux oesophagitis with lansoprazole 30 mg was as effective as with omeprazole 40 mg with respect to healing as well as symptom relief [12]. Furthermore, it has been shown that the 15-mg and 30-mg lansoprazole doses do effectively prevent recurrence of erosive oesophagitis in a 12-month period [13].

At present, the role of the drug is also being investigated in *H. pylori* eradication therapy, showing that one-week triple therapy (lansoprazole in combination with amoxicillin and clarithromycin) and four-day quadruple therapy (lansoprazole in combination with bismuth, tetracycline and metronidazole) have high cure rates of respectively over 90% and 98% [1, 14, 15].

Incidences of adverse reactions as estimated from clinical trial data are similar to those of other PPIs and H_2-receptor antagonists [2, 4, 7, 11]. The most common events include headache (4.7%), diarrhoea (3.2%), abdominal pain (2.2%), pharyngitis (1.8%) and skin disorders (1.7%) [1].

From clinical trials, it can be stated that lansoprazole is highly effective and well tolerated by most patients, although data from treatment in 'daily practice' are still scarce. Clinical research only gives partial insight into the effectiveness, safety and patterns of use of a drug such as demographics, prescription indications, dosage regimens, co-morbidity, drug exposure and co-medication [16]. Limitations of clinical trials include the relatively small number of patients, patients having less co-morbidity and/or co-medication, a short duration of the studies and different circumstances under which the drug is administered. These limitations have fostered the development of this prospective follow-up study with lansoprazole. In order to design sound post-marketing follow-up studies it is essential not to influence the decisions of a physician prescribing drug therapy. Guidelines for Safety Assessment of Marketed Medicines (SAMM) have been developed by a joint committee with members with a clinical, regulatory, academic or pharmaceutical industry background in order to provide basic rules to ensure good study design. This study was according to these SAMM guidelines. The aim of this study was to assess the safety and effectiveness of lansoprazole in a population composed by naturally occurring groups of users and to evaluate the patterns of use of lansoprazole in daily practice.

MATERIALS AND METHODS

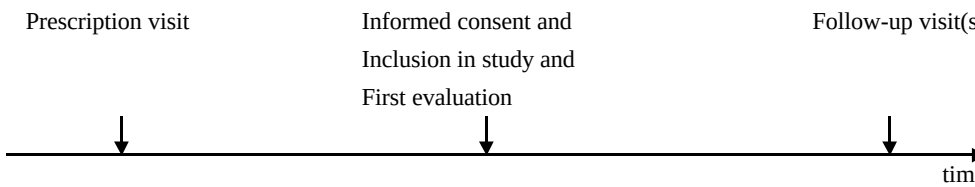
This prospective, open, observational follow-up study was carried out by GPs and specialists (internists/gastro-enterologists) in naturally occurring users of lansoprazole in the Netherlands during the first two years after marketing (1994-1995).

Design

The study protocol was designed according to the SAMM guidelines [17] including a population as representative as possible of the general population, a non-interventional design and a clear separation in time between the prescribing of the drug and the inclusion of the patient in the study (illustrated in Figure 1). The protocol has been approved by the Medical Ethical Committee of the Utrecht University Medical Centre. The highest standards of professional conduct and confidentiality were maintained throughout the study. GPs could include a maximum of 20 patients per two years follow-up time, while specialists were allowed to incorporate not more than 50 patients. All lansoprazole prescribing

GPs, internists and gastro-enterologists were asked to participate. In order to avoid inclusion bias participating physicians and pharmacists were remunerated with only a modest fee equivalent to the reimbursement of their time spent to complete the record forms or generate the medication histories. Additional safety evaluation was conducted analysing patients with adverse events (cases) compared to patients without adverse events (controls) from all lansoprazole users in this study.

Figure 1
Procedure of inclusion of patients in study



Patient Selection

All patients having used or using lansoprazole could be included in the study at the first or any later follow-up visit after lansoprazole was prescribed. Patients agreed to participate by giving their written informed consent allowing to have access to all relevant clinical and medication data and storage and analyses of these data. No further selection criteria were considered. So all lansoprazole users could be included, independent of e.g. age, indication of use, co-morbidity, use of co-medication. To maintain patient anonymity, patients were identified by an identification code only. All data and documents related to patients included, were kept in strict confidence and in accordance with the official privacy regulations.

Measurements

Data were collected at the visit of inclusion and at each follow-up visit during lansoprazole therapy with a maximum follow-up of two years by reviewing the medical file and by patient-questionnaire. The data collection did not in any way

influence normal procedures. No additional diagnostic tests were requested from the physician regarding the diagnosis and measurement of effectiveness.

Patient characteristics including age, gender, smoking habits, alcohol intake and pregnancy were recorded. Information obtained on medical status at the time of first lansoprazole prescription included indication, endoscopic examination (if available) and relevant medical history. Characteristics and patterns of use of lansoprazole that were recorded included type of prescriber, daily dose of lansoprazole, previous therapy for acid-related complaints, concomitant over-the-counter (OTC) therapy and date of end of therapy. Effectiveness of lansoprazole therapy was recorded analogous to normal procedures at the physician: changes in the indication-related complaints by the patient, assessment of change in general well-being of the patient and the assessment by the physician on whether a patient was cured from the indication for which lansoprazole was prescribed.

The procedures on which the assessment of effectiveness by the physician was based (endoscopy, symptoms, x-rays, other) were recorded, however no standardised symptom scores were collected, adhering to daily practice routines. To assess safety-aspects of use of lansoprazole all (adverse) events (including onset, duration, severity, association with lansoprazole, action taken) irrespective of being linked to lansoprazole therapy were documented during the follow-up period. The severity and association of adverse events were reported assessed by the physician.

Complete medication histories of patients over six months before starting therapy and during follow-up were retrieved at the local pharmacy. Computerisation of pharmacy records, and thus the compilation of medication histories, is almost universal in the Netherlands. The majority of patients (78%) is designated to a single pharmacy for all reimbursed prescription drugs [18]. Prescribed drugs were coded according to the Anatomical-Therapeutic-Chemical (ATC) classification [19].

To ensure the collection of accurate, consistent, complete and reliable data participating physicians were instructed and monitored in completing the forms at regular intervals. Data verification checks and cross checks were performed after data-entry by trained datamanagers. Inquiries were made about inconsistencies, incorrect data, and missing data. Missing values remained in 0.1%.

Analysis

Results were tabulated in absolute values and/or percentages. Baseline comparisons were calculated using χ^2-tests, crude and adjusted odds ratios with a confidence interval of 95%. Adjusted odds ratios were calculated using conditional logistic regression. Statistical significance was assumed at p-values < 0.05. All statistical analyses were performed using SAS and EGRET statistical packages.

RESULTS

Patient enrolment started in January 1994 following the introduction of lansoprazole in The Netherlands in September 1993. In total 166 specialists and 595 GPs agreed to participate of which actually respectively 70% (n=117) and 63% (n=374) included patients in this study. Main reasons for non-participation were lack of time, lack of interest and few lansoprazole prescriptions. The voluntary participation rate of pharmacists was 74.4%. Over a period of 24 months, follow-up data of 5,741 patients were gathered. Of these patients, 72 (1.3%) were not evaluable for analysis (either no informed consent was obtained or no separation in time between first prescription and inclusion in study was maintained) thus making 5,669 eligible patients for the study. An average number of 9 patients were included per GP and 19 patients per specialist.

Demographics

In Table 1 the general characteristics of the study population are shown. Overall mean age was 54.2 years (range: 14-96); men had a mean age of 51.2 years (range: 14-94), while women were significantly older with a mean age of 56.9 years (range: 15-95).
Four patients included in the study used lansoprazole during their pregnancy. One patient used lansoprazole during the first month of her pregnancy, one during the sixth month, one intermittently during the sixth and ninth month and one during the last three months. All patients gave birth to healthy infants. The majority of the included patients (71.6%) were non-smokers. Only 10.6% were heavy smokers (≥ 15 cigarettes/cigars per day). Most patients reported no use of alcohol (56.6%) or less than 5 units of alcohol per day (41.1%). Alcohol use was reported twice as frequent in men compared to women and was highest in patients of 30-60 years of age in both sexes.

Table 1
General characteristics of the study population

	N=5,669	%
Men	2,751	48.5
Women	2,918	51.5
Age (years)		
0-30	398	7.0
30-45	1,309	23.1
45-60	1,847	32.6
60-75	1,573	27.7
> 75	542	9.5
Co-morbidity at the time of lansoprazole prescription known from physician		
None	3,347	59.0
Gastrointestinal (excl acid-related disorders)	409	7.2
Cardiovascular	499	8.8
Endocrine	251	4.4
Respiratory	184	3.2
Musculoskeletal	154	2.7
Psychiatric	119	2.1
Co-medication at the time of lansoprazole prescription known from pharmacy *	4,219	100.0
None	2,169	51.4
Gastrointestinal (excl lansoprazole)	1,041	24.6
Cardiovascular	488	11.6
Endocrine	207	4.9
Respiratory	225	5.3
Musculoskeletal	216	5.1
Psychiatric	721	17.1

* Of 1,450 patients (25.6%) no information from pharmacy was available.

Co-morbidity was assessed by the physician at the date of inclusion of the patient. Furthermore, co-medication as found in medication histories collected in the pharmacy was used as an indication of co-morbidity (Table 1). Gastrointestinal (other than acid-related disease) co-morbidity was highly prevalent in this population (7.2%). Cardiovascular (8.8%), endocrine (4.4%) and respiratory disease (3.2%) were also frequently seen. The most frequently reported underlying diseases included hypertension (5.1%), asthma /COPD (2.4%) and diabetes mellitus (2.2%). Co-morbidity reported by the physician was in general consistent with the medication histories derived from the pharmacists. However, the physicians reported psychiatric co-morbidity in 2.1% of the patients, whereas according to the pharmacies 16.7% used psychiatric drugs. This can be explained by the fact that frequently used drugs for sleeping disorders and anxiety were scored in the category psychiatric co-medication, while physicians did not report this as co-morbidity.

Patterns of use

Patients had an average follow up of 120 days, during which they used lansoprazole for an average period of 98 days. The most frequently reported indication (Table 2) for which lansoprazole was prescribed was reflux oesophagitis (reported in 55.1% of all patients), followed by 'gastritis' (26.8%) and duodenal ulcers (11.4%). Furthermore, the combined indication reflux oesophagitis plus 'gastritis' was frequently reported (7.5%). In 8.5% of all patients the lansoprazole prescription was part of a *H. pylori* eradication therapy. This was most frequently seen in patients with 'duodenitis' (26.5%), duodenal ulcers (25.2%), and gastric ulcers (19.4%). In comparison with GPs, specialists prescribed lansoprazole significantly more often in patients with gastric ulcers, reflux oesophagitis, 'duodenitis' and as part of *H. pylori* eradication therapy and less frequent in patients with 'dyspepsia', peptic ulcers and 'gastritis'. Duodenal ulcers were equally often diagnosed by GPs and specialists. In 71.0% of the patients lansoprazole was prescribed for indications mentioned in the information leaflet. In the other 29.0% lansoprazole was prescribed for indications not registered in The Netherlands such as 'gastritis', 'dyspepsia' and 'duodenitis'.

Little over half of the diagnoses (50.3%) were based on an endoscopy. In 85.3% of the patients evaluated by specialists and in 27.4% of the patients evaluated by GPs an endoscopy was performed. In patients with peptic ulcers or reflux

oesophagitis diagnosis was based on an endoscopy in 53.3% of all cases, while in patients with reported 'gastritis', 'duodenitis' or 'dyspepsia' endoscopy was used in only 39.2% of the cases.

Table 2
Indication of lansoprazole use at inclusion

	Total % (N=5,669)	GPs % (N=3,425)	Specialists % (N=2,244)	
Indication†				
Reflux oesophagitis	55.1	51.2	60.9	**
Duodenal ulcer	11.4	11.6	11.0	
Gastric ulcer	3.8	2.2	6.4	**
Peptic ulcer	3.2	4.7	0.9	**
'Gastritis'	26.8	31.4	19.8	**
'Dyspepsia'	11.2	12.9	8.5	**
'Duodenitis'	4.7	2.7	7.6	**
Other	9.3	8.2	10.9	**
Endoscopy performed	50.3	27.4	85.3	**
Part of *H. pylori* eradication	8.5	6.0	12.4	**

* p-value < 0.05 comparing specialists with GPs

** p-value < 0.01 comparing specialists with GPs

† Totals may exceed 100% because of multiple answers possible

In 60.4% of the patients lansoprazole was evaluated by a GP, in 32.9% by an internist, in 6.1% by a gastro-enterologist and in 0.5% of patients by another specialist. Of all patients 95.3% had a daily regimen of 30 mg prescribed. Patients with a daily dose of ≤15 mg (0.3%) had prescriptions of 30 mg lansoprazole every two or three days, or on demand. In 4.3% of patients a daily dose of ≥60 mg was prescribed, of which 41.3% were prescriptions for the eradication of *H. pylori.* A majority of the patients (76.4%) still used lansoprazole at the time of first evaluation. Patients who had discontinued therapy before the first evaluation took place (23.6%) had used the drug with a mean duration of 24 days and 42.1% of these patients stopped lansoprazole use within the first two weeks.

Table 3
Previous acid-related drug use in 5,669 lansoprazole users

	Total % (N=5,669)	GPs % (N=3,425)	Specialists % (N=2,244)	
None	8.9	10.3	7.0	**
Previous use of lansoprazole	16.0	18.5	14.2	**
Other previous acid related drug use†				
Antacid	8.2	10.3	5.1	**
H_2-receptor antagonist	45.4	45.1	45.9	
Other PPI	11.0	6.8	17.6	**
Prokinetic	8.4	9.7	6.3	**
Mucosaprotective	5.5	6.5	4.1	**
Other	2.4	2.0	2.9	*

* p-value < 0.05 comparing specialists with GPs

** p-value < 0.01 comparing specialists with GPs

† Totals may exceed 100% because of multiple answers possible

The majority of the patients included in the study were first time users of lansoprazole (83.2%). Previous treatment with omeprazole was seen in 11.0% of all patients. In general, the patients included in the study had an extensive history of acid-related drug use (Table 3). 91.1% of the patients had been treated with acid-related drug therapy before, mainly H_2-receptor antagonists (45.4%). Patients with duodenal ulcers and patients with 'duodenitis' had in 55.1% a history of H_2-receptor antagonists use. Dyspeptic patients were characterised by a high previous use of prokinetics (14.7%).

Effectiveness

Effectiveness of lansoprazole was measured using three parameters: the change in indication-related complaints reported by the patients, the change in general well being of the patient and the assessment by the physician on whether the indication for lansoprazole therapy had disappeared.

Figure 2
Effectiveness of lansoprazole use

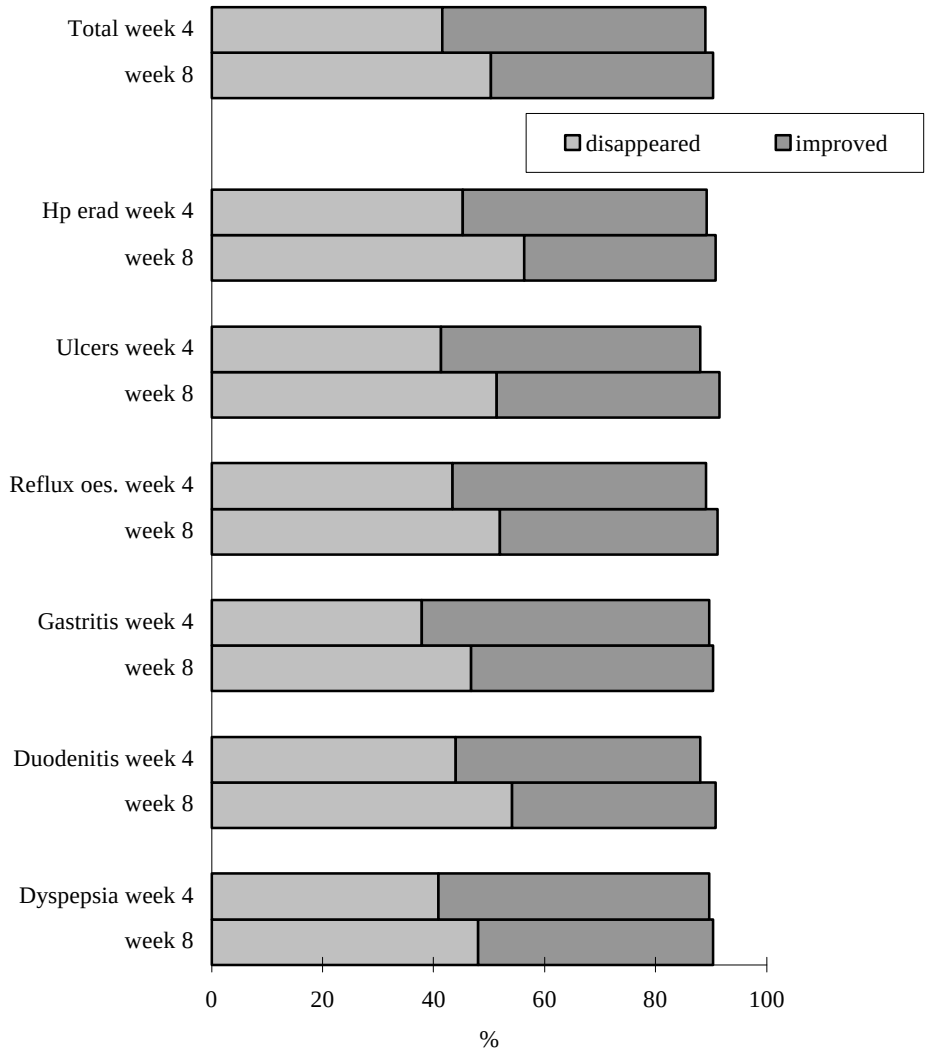


Table 4
Adverse events in patients receiving lansoprazole

	N=5,669	%
Patients reporting adverse events		
No adverse events	4,541	80.1
1 adverse event	771	13.6
2 adverse events	234	4.1
> 2 adverse events	123	2.2
Total number of reported adverse events	1,666	100
Onset of adverse events (per event)		
Within 1 day	363	21.7
1-13 days	613	36.8
≥14 days	587	35.2
Unknown	103	6.2
Severity of adverse events (per event)		
Mild	774	46.5
Moderate	646	38.8
Severe	240	14.4
Unknown	6	0.4
Association of adverse event with lansoprazole (per event)		
Unlikely	353	21.1
Possible	822	49.3
Probable	486	29.2
Unknown	5	0.3
Action taken (per event)		
None	938	56.3
Dose reduction/stop of therapy	594	35.7
Switch of therapy	116	7.0
Other action	11	0.7
Unknown	7	0.4

As can be seen in Figure 2 patients reported their indication-related complaints to have disappeared or improved at week 4 in 88.9% of patients and at week 8 in 90.5% of patients. There were no significant differences in effectiveness between the various indications. In patients previously using omeprazole, complaints disappeared or improved in 81.2% of patients at week 4 and in 83.5% of patients in week 8. No differences were seen in disappearance or improvement of complaints between patients switched directly from omeprazole to lansoprazole and patients with a period of 1 week to 6 months between previous omeprazole use and lansoprazole therapy.

General well being of the patients was improved in 79.9% of patients at week 4 compared to before start of lansoprazole therapy and in 82.0% of patients at week 8. No significant differences between the indications were found. Patients were declared cured by their physicians in 35.9% of the cases at week 4 and in 46.8% at week 8. Their was a significantly higher number of patients with 'duodenitis' declared cured at week 4, 40.7% ($p<0.01$) and at week 8, 53.6% ($p<0.01$). The judgement on whether a patient was cured was almost exclusively based upon symptomatology alone, 94.6%. Only in 5.1% it was based on additional endoscopy or x-rays.

Safety

Of all lansoprazole users 80.1% reported no adverse events during drug exposure. A minority of 2.2% reported more than two adverse events during use. The onset of the events was soon after start of the therapy, in 21.7% at day one and in 36.8% at day 2 to 13 (Table 4). Of all adverse events 29.2% was probably related to the lansoprazole exposure, as reported by the physician. In a majority of the events (56.3%) no action was taken and in 35.7% the lansoprazole dosage was reduced or discontinued. According to the physician nearly all adverse events were of mild (46.5%) or moderate (38.8%) severity, whereas 14.4% included severe adverse events.

In a further analysis (Table 5) patients with adverse events were compared with patients without adverse events. Patients with adverse events, compared to patients without adverse events, were significantly more often female. Alcohol consumption of 1-4 units per day was seen significantly more often in patients with adverse events. Previous use of PPIs or mucosaprotectives and concomitant use

of OTC-therapy was significantly more common in patients with adverse events compared to patients without adverse events.

Table 5
Co-factors of lansoprazole users with and without adverse events

	Adverse events		Odds ratio	
	yes % (N=1,123)	no % (N=4,546)	crude (95% CI)	adjusted** (95% CI)
Men	43.5	49.8	(reference)	(reference)
Women	56.5	50.2	1.3 (1.1-1.5)	1.4 (1.2-1.6)
Age (years)				
0-30	5.5	7.0	(reference)	(reference)
30-45	19.0	23.4	1.0 (0.8-1.4)	0.9 (0.7-1.3)
45-60	32.9	32.4	1.3 (1.0-1.7)	1.1 (0.8-1.4)
60-75	32.2	27.3	1.5 (1.1-2.0)	1.1 (0.8-1.5)
> 75	10.3	9.9	1.3 (0.9-1.8)	1.0 (0.7-1.4)
No drinking	52.4	57.7	(reference)	(reference)
< 5 units/day	45.5	40.0	1.3 (1.1-1.4)	1.4 (1.2-1.6)
≥ 5 units/day	1.9	2.2	0.9 (0.6-1.5)	1.0 (0.6-1.4)
Evaluator GP	53.2	62.2	(reference)	(reference)
Evaluator specialist	46.8	37.8	1.5 (1.3-1.7)	1.4 (1.2-1.6)
Indication*				
Reflux oesophagitis	61.4	53.5	1.4 (1.2-1.6)	1.2 (1.0-1.5)
Duodenal ulcer	9.2	11.9	0.7 (0.6-0.9)	0.7 (0.6-1.0)
Gastric ulcer	3.3	4.0	0.8 (0.6-1.2)	0.9 (0.7-1.4)
Peptic ulcer	2.0	3.5	0.5 (0.4-0.9)	0.6 (0.4-0.9)
'Gastritis'	25.6	27.1	0.9 (0.8-1.1)	1.0 (0.9-1.2)
'Dyspepsia'	10.4	11.3	0.9 (0.7-1.1)	1.0 (0.8-1.3)
'Duodenitis'	5.0	4.6	1.1 (0.8-1.5)	1.1 (0.8-1.5)

* Compared to patients with any other indication

** Adjusted with conditional logistic regression, including all listed co-factors

Table 5
(continued) Co-factors of lansoprazole users with and without adverse events

	Adverse events		Odds ratio	
	yes % (N=1,123)	no % (N=4,546)	crude (95% CI)	adjusted† (95% CI)
Previous acid related drug use*				
Antacid	7.1	8.5	0.8 (0.6-1.1)	0.8 (0.6-1.0)
H_2-rec.antagonist	49.1	44.5	1.2 (1.1-1.4)	1.1 (0.9-1.3)
PPI	17.8	12.9	1.5 (1.2-1.7)	1.2 (1.0-1.5)
Prokinetic	8.4	8.4	1.0 (0.8-1.3)	0.9 (0.7-1.2)
Mucosaprotective	7.1	5.1	1.4 (1.1-1.9)	1.4 (1.0-1.8)
OTC-use	9.5	5.7	1.7 (1.4-2.2)	1.5 (1.2-2.1)
Daily dose 60 mg	4.6	4.7	1.0 (0.7-1.4)	0.9 (0.7-1.3)
Co-morbidity				
Gastrointestinal**	5.2	3.7	1.4 (1.1-1.9)	1.5 (1.1-2.0)
Cardiovascular	15.2	11.1	1.4 (1.2-1.7)	1.4 (1.1-1.7)
Endocrine	5.2	4.3	1.2 (0.9-1.6)	1.0 (0.7-1.4)
Respiratory	3.9	3.4	1.2 (0.8-1.6)	1.1 (0.8-1.6)
Musculoskeletal	4.2	3.0	1.4 (1.0-1.9)	1.3 (0.9-1.9)
Psychiatric	1.8	2.5	0.7 (0.4-1.1)	0.7 (0.4-1.2)

* Compared to patients with no or other previous acid related drug use

** Excluding acid-related disorders

† Adjusted with conditional logistic regression, including all listed co-factors

Reflux oesophagitis showed to be significantly more prevalent in patients with adverse events compared to patients without adverse events. Duodenal and peptic ulcers on the other hand were significantly less prevalent in patients reporting adverse events. Specialists evaluated significantly more patients with adverse events compared to GPs. In addition, in 48.6% of the patients with adverse events co-morbidity was present compared to 39.0% of patients without adverse events (adjusted OR (95% CI): 1.5 (1.1-1.9)). Non acid-related gastrointestinal co-

morbidity and cardiovascular disorders showed a significant association with the occurrence of adverse events.

Distributions of the most frequently (>1%) observed adverse events reported in our study population and expected frequencies of the most frequently reported adverse events from clinical trials are listed in Table 6.

Table 6
Adverse events reported in 5,669 patients receiving lansoprazole compared with expected frequencies on basis of clinical trial data [1]

Frequently reported adverse events	Expected %	Observed %	
Gastrointestinal			
Diarrhoea	3.2	4.1	**
Abdominal pain	2.2	1.6	*
Nausea	1.4	2.6	**
Constipation	1.1	1.1	
Central nervous system			
Headache	4.7	2.9	**
Dizziness	1.0	2.2	**
Respiratory tract			
Pharyngitis	1.8	0.0	
Rhinitis	1.3	0.0	
Cough	0.4	0.1	*
Other			
Skin disorders	1.7	1.8	
Anxiety	0.2	0.1	
Depression	0.2	0.1	
Myalgia	0.4	0.2	*

* p-value < 0.05

** p-value < 0.01

Diarrhoea, headache and nausea were the most frequently reported adverse events. When compared to clinical data (expected frequencies), dizziness, nausea and diarrhoea showed up significantly more in the study patients. On the other hand headache, cough, myalgia and abdominal pain were reported less frequently than expected from clinical trials.

DISCUSSION

The main objective of this study was to assess the safety and effectiveness of lansoprazole in a population composed by naturally occurring groups of users and to evaluate the pattern of use of the drug in daily practice in the Netherlands. Data were collected of 5,669 lansoprazole users evaluated by 374 GPs and 117 specialists spread over the Netherlands.

The results indicate that lansoprazole was predominantly prescribed in men of 30-60 years of age and women of 45-75 years of age. This distribution reflects the distribution of a population with acid-related disorders [20].

At the start of the study lansoprazole 30 mg was registered in The Netherlands for the treatment of reflux oesophagitis and duodenal and gastric ulcers. In this study lansoprazole was prescribed in 71.0% of the patients for such indications. However, results indicate that ‘gastritis’ and ‘dyspepsia’ were also frequently reported indications for which lansoprazole was prescribed, besides the registered indications. In 72.6% of the patients included by GPs no endoscopy was ever performed versus 14.7% of the patients evaluated by specialists. In general specialists perform more diagnostic tests, such as endoscopy, compared to GPs. This might explain the different frequencies reported in diagnosing reflux oesophagitis and ‘gastritis’ between GPs and specialists.

In this study in more than 25% of the patients with duodenal ulcers lansoprazole was used as part of *H. pylori* eradication therapy. The number of patients in which lansoprazole was used as part of *H. pylori* eradication therapy increased in time during the study and was higher in patients evaluated by specialists than GPs. In recent literature is described that the prevalence of *H. pylori* is up to 100% in patients with duodenal ulcers indicating *H. pylori* eradication therapy in all of these patients [21].

The standard prescribed daily dose in this study was as mentioned in the information leaflet 30 mg. In a few patients 60 mg per day was prescribed. In these patients the prescription was frequently part of a *H. pylori* eradication therapy.

Furthermore, users of lansoprazole in daily clinical practice showed to be patients with an extensive history of previous acid-related treatment, mainly H_2-receptor antagonists. These previous users might be switched to lansoprazole due to low efficacy and/or occurrence of adverse events with previously used acid-related drugs.

Measured as improvement or disappearance of indication-related complaints, therapy with lansoprazole proved to be highly effective. Over 90% of the patients experienced a disappearance or improvement of indication-related complaints at week 8, independently of the indication. These results are comparable with the results of clinical trials [1]. Characteristic of a pharmacoepidemiological study is the natural setting in which data are collected. Therefore, unlike in clinical trials, no testing of effectiveness beyond normal procedures in daily clinical practice took place. In clinical trials however, there is a strict patient selection resulting in a study group which differs greatly from the users of newly registered drugs in a natural setting [16]. The effectiveness found in this study is high taking into account the fact that patients were only endoscopically examined in 50.3%, that indications differed from the indications for which lansoprazole is registered in 29% and that complicated patients were included (e.g. with co-morbidity, co-medication, previous acid-related drug use). In previous omeprazole users the effectiveness was lower. It is unclear whether the physician switched therapy from omeprazole to lansoprazole because of the low effectiveness during omeprazole use. Further research on switching of therapy may provide interesting information on patients showing lack of effectiveness, low compliance or adverse drug reactions as a reason for switching.

In various clinical trials [4, 10] patients using lansoprazole 30 mg reported adverse events in 16.9-29.2% and patients using omeprazole 20 mg in 23.8-32.8%, whereas in this study 19.9% reported one or more adverse events, making the results comparable. The overall safety profile in this study was similar to the profile of events of clinical trials with lansoprazole as illustrated in Table 6 and similar to the profile of an analysis of 68 clinical trials with omeprazole [1, 11]. In general the adverse events during lansoprazole use were mild and self-

limiting. No serious adverse events related to the drug were observed in the study group. Compared to clinical trials with lansoprazole diarrhoea, nausea and dizziness showed up significantly more frequently and abdominal pain and headache less frequently in this study [1]. All women, who had used lansoprazole during their pregnancy, gave birth to healthy infants. Compared to clinical trials there were few respiratory tract, psychiatric and musculoskeletal adverse events. In this study with complicated patients and a non-interventional design adverse events might be more or less frequently reported compared to clinical trials. To investigate this more specifically two additional studies are set up regarding the occurrence of headache and diarrhoea as adverse event in lansoprazole users.

It became clear that lansoprazole users reporting adverse events have a different 'profile' compared to lansoprazole users reporting no adverse events. The profile of lansoprazole users reporting adverse events can be characterised as females, moderate alcohol users, with concomitant OTC-use, and the presence of co-morbidity. With this information, patients can be better instructed and informed about the occurrence of adverse events while using lansoprazole.

In conclusion the patterns of use of lansoprazole in daily practice differ in a small part of the patients from the information given in the information leaflet. The drug is also used in patients for the treatment of 'gastritis', 'dyspepsia', 'duodenitis', and the eradication of *H. pylori.* Furthermore it is also prescribed in 60 mg dosage regimens, in a few pregnant women and in complicated patients with co-morbidity and co-medication. Nevertheless, therapy with lansoprazole proved to be highly effective in nearly all naturally occurring lansoprazole users with a variety of acid-related complaints. In 19.9% of the patients adverse events were reported. Overall these adverse events were mild and self-limiting. Specific patient groups were identified with a higher risk to develop adverse events.
Because of the setting in daily clinical practice and the large number of included patients, it can be stated that this study population of naturally occurring groups of users differed from the population of patients studied in premarketing clinical trials. However, the findings on safety and effectiveness were comparable with results of clinical trials with lansoprazole.

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Chapter 2.2

Which determinants are associated with non-response in proton pump inhibitor users? A study of lansoprazole therapy

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SUMMARY

Background: Proton pump inhibitors (PPI) demonstrate high healing rates of 85-98% in clinical trials. Due to the limited knowledge regarding response and non-response to lansoprazole postmarketing and for the reason that resistance to PPIs is scarce, we investigated determinants possibly associated with non-response.
Methods: Data were used from a prospective, open label, observational follow-up study in which 10,008 lansoprazole users were followed over time. The study was designed according to the SAMM guidelines. A matched nested case-control design was used to compare non-responding (cases) and responding (controls) lansoprazole users. Non-response was defined as worsening or non-improvement of symptoms at the first evaluation after at least 8 weeks of use, response as disappearance or improvement of symptoms within 8 weeks of use. Controls were matched for the evaluating physician.
Results: A total of 186 non-responders and 372 responders of PPI treatment were identified as cases and controls. Age of over 60 years, heavy smoking and previous use of PPIs were significantly more common in non-responding patients compared with responding patients. There were no differences found between the reported diagnosis regarding response.
Conclusion: In daily clinical practice, previous use of PPIs, heavy smoking and an age > 60 years were significantly associated with non-response to treatment with lansoprazole. Previous use of PPIs in non-responding patients might suggest resistance to PPIs. The knowledge that non-response drives non-response may encourage physicians to follow PPI users with previous PPI use more closely.

INTRODUCTION

In the Netherlands, PPIs are registered for use in patients with gastric ulcer, duodenal ulcer and/or GERD. In clinical trials PPIs demonstrated high healing rates of 85 to 98% for different indications [1, 2]. PPIs selectively inhibit the gastric parietal cell membrane enzyme, H+/K+-ATPase ('the proton pump') inducing reduction of gastric acid secretion. This pharmacological profile accomplishes the high healing rates and rare resistance [1, 3]. Because prescribing physicians may apply other selection criteria to patients in daily clinical practice when compared with physicians participating in clinical trials, effectiveness when used for indications or in dosages other than initially tested may differ from efficacy found in clinical trials. In an initial observational study we found that indication-related complaints disappeared or improved in 90.5% of patients after 8 weeks of lansoprazole use [4]. In clinical trials, patients have to meet strict selection criteria, meaning that for example, only patients with endoscopically proven indications are included, whereas patients with co-morbidity, co-medication and/or previous use of acid related drugs are often excluded [5]. Furthermore, compliance in clinical trials is often not comparable with daily practice. In daily clinical practice, PPIs will also be used in patients with unlabelled and/or unproved diagnosis, in atypical dosages and in complex situations for example, patients with previous therapy, co-morbidity and/or co-medication [6-8]. Besides selection of patients, the assessment of response in clinical trials will also often differ from the assessment in daily clinical practice. In daily clinical practice the response is nearly always based on symptoms and less frequently on endoscopies, whereas in clinical trials response is not only symptomatically assessed (as changes in symptoms such as epigastric pain, heartburn, dysphagia), but endoscopies are often part of the protocol [9]. Due to the limited knowledge regarding response and non-response to lansoprazole postmarketing and for the reason that resistance to PPIs is scarce, we investigated determinants possibly associated with non-response, such as compliance, diagnosis and response to previous treatment [3].

MATERIALS AND METHODS

Design and selection of subjects

A prospective, open label, observational follow-up study was conducted in the Netherlands in 10,008 lansoprazole users in daily practice during the first four

years after marketing (January 1994 until April 1998). The aim of the study was to evaluate the safety, efficacy and the patterns of daily use of lansoprazole [4]. Informed consent was obtained from all patients. No additional in- or exclusion criteria were considered. A case-control design was used to investigate non-response. Response was evaluated by changes in symptoms (disappearance, improvement, remaining the same, worsening) as assessed by the physician. Cases were defined as non-responding lansoprazole users and controls as responding lansoprazole users. The non-responders (N=195) consisted of patients with at least 8 weeks of use, and no improvement or worsening of symptoms at the first evaluation after 8 weeks. The responders (N=9,159) included patients in which an improvement or disappearance of symptoms was reported within 8 weeks of use, or at the first evaluation after 8 weeks of use. Patients that discontinued therapy within 8 weeks with no improvement or worsening of symptoms (N=479) or had a follow-up of less than 8 weeks after first use with no improvement or worsening of symptoms (N=175) were excluded from this analysis.

Controls were matched for the evaluating physician in order to limit observer bias with a case-control ratio of 1:2 [10]. The preceding patient of the evaluating physician was defined as matched control. In case a so-defined preceding control patient was not available, the next available patient of the same physician served as the control. For a small subset of cases and controls an additional case-control study was performed and matched by physician in a ratio of 1:1.

Measurements

Data were collected during lansoprazole therapy at visits after prescription of lansoprazole by reviewing the medical file and by patient questionnaire. The data collection was designed not to influence normal procedures. The following details were recorded for all patients: gender, age, alcohol intake, smoking habits, prescriber and evaluator, indication, daily dose, co-morbidity, adverse events, previous use of acid reducing drugs and response to lansoprazole therapy. Three different primary diagnoses were distinguished: peptic ulcer, gastro-oesophageal reflux disease and other diagnoses (e.g. ‘gastritis’, ‘duodenitis’). No additional diagnostic tests were requested from the physician with regard to the primary diagnosis. The physician recorded the response analogous to normal procedures as changes in symptoms (disappeared, improved, remained equal, worsened). In addition, more specific information was collected of a subset of 33 non-

responding cases and 33 responding controls matched by physician. The details as stated by the physician included the primary indication of PPI use, if available conclusions of performed endoscopies, any history of gastric surgery and previous treatments and outcomes of acid related complaints the year before initial PPI therapy. From the patient, present symptoms (using a standardised symptom checklist) before starting PPI therapy were scored, the response to lansoprazole therapy was questioned (documented as disappeared, improved, remained equal, worsened), and discontinuation due to non-response was inquired. Compliance was assessed through the following questions to the patient: the prescribed lansoprazole dose, the frequency of missing capsules (scored as never, sometimes, regular, often) and maximum number of days of missing capsules (if more than one day).

Analysis

Results were tabulated in absolute values and percentages. Subsets were analysed according to a matched case-control design with a 1:1 or 1:2 ratio for cases and controls. Baseline comparisons were calculated using crude and adjusted odds ratios with a confidence interval of 95%. Adjusted odds ratios were calculated using conditional logistic regression. Statistical significance was defined at p-value < 0.05. All statistical analyses were performed using SAS and EGRET statistical packages.

RESULTS

A total of 10,008 patients were evaluated regarding determinants associated with non-response. We identified 186 non-responders and 372 responders of lansoprazole treatment by matching on evaluating physician. A case control analysis was set up to make comparisons among non-responders and responders.

Of all the 558 patients, 62.9% were evaluated by specialists and 37.1% by general practitioners (GPs).

In Table 1, the distribution of determinants among cases and controls is presented. Mean age of cases was 56.1 years (min. 19.0, max. 90.0) and of controls 54.2 years (min. 16.0, max. 91.0). Gender, alcohol use, daily dose of lansoprazole and co-morbidity were equally distributed between non-responding and responding patients.

Table 1
Characteristics of cases (non-responders) and controls (responders)

	Cases		Controls		Crude OR	Adjusted OR
	N=186	(%)	N=372	(%)	(95% CI)	(95% CI)
Men	86	(46.2)	175	(47.1)	(reference)	(reference)
Women	100	(53.8)	197	(53.0)	1.0 (0.7-1.5)	1.1 (0.7-1.6)
Age (years)						
0-30	5	(2.7)	26	(7.0)	(reference)	(reference)
30-45	45	(24.2)	88	(23.7)	2.4 (0.9-6.7)	2.6 (0.9-7.6)
45-60	55	(29.6)	113	(30.4)	2.4 (0.9-6.6)	2.5 (0.9-7.1)
60-75	53	(28.5)	104	(28.0)	2.5 (0.9-6.8)	3.0 (1.0-8.8)
> 75	28	(15.1)	41	(11.0)	3.2 (1.1-9.2)	4.0 (1.3-12.4)
Alcohol use	67	(36.0)	150	(40.3)	0.8 (0.5-1.2)	0.7 (0.4-1.2)
No smoking	130	(69.9)	284	(76.3)	(reference)	(reference)
<15 units/day	36	(19.4)	67	(18.0)	1.2 (0.7-1.9)	1.6 (0.9-2.8)
≥15 units/day	20	(10.8)	21	(5.6)	2.0 (1.1-3.9)	2.5 (1.2-5.1)
Daily dose						
30 mg	166	(89.2)	337	(90.6)	(reference)	(reference)
60 mg	19	(10.3)	35	(9.4)	1.1 (0.6-2.2)	1.0 (0.5-2.1)
Indication						
GERD	96	(51.6)	207	(55.7)	0.9 (0.6-1.4)	0.9 (0.6-1.5)
Ulcer	27	(14.5)	49	(13.2)	1.4 (0.9-2.3)	1.4 (0.8-2.5)
Other	55	(29.6)	111	(29.8)	1.0 (0.8-1.9)	1.0 (0.8-1.9)
Co-morbidity						
Gastrointestinal (ex acid)	30	(16.1)	68	(18.3)	0.8 (0.5-1.4)	0.7 (0.4-1.3)
Cardiovascular	21	(11.3)	47	(12.6)	0.9 (0.5-1.5)	0.8 (0.4-1.4)
Endocrine	11	(5.9)	26	(7.0)	0.8 (0.4-1.7)	0.8 (0.3-1.7)
Musculoskeletal	8	(4.3)	19	(5.1)	1.3 (0.6-2.7)	1.2 (0.6-2.7)
Respiratory	13	(7.0)	20	(5.4)	0.8 (0.4-2.0)	1.0 (0.4-2.6)
Psychiatric	9	(4.8)	12	(3.2)	1.6 (0.6-4.3)	2.1 (0.7-6.1)
Previous drug use						
H_2-receptor antagonist	76	(40.9)	165	(44.4)	0.8 (0.6-1.2)	1.0 (0.6-1.5)
Any PPI	84	(45.2)	80	(21.5)	3.6 (2.3-5.6)	4.1 (2.6-6.5)

The distribution of indication for therapy, whether or not confirmed by endoscopy, was similar for cases and controls. An age > 60 years showed to be significantly associated with non-response; for the age category 60-75 years the adjusted OR (95% CI) was 3.0 (1.0-8.8), while for the age category > 75 years the adjusted OR (95% CI) was 4.0 (1.3-12.4). Heavy smoking (≥15 units/day) was significantly more frequent in cases as compared with controls (adjusted OR (95% CI): 2.5 (1.2-5.1)).

Furthermore, previous use of PPIs was very common in cases (45.2%) compared to controls (21.5%) (adjusted OR (95% CI): 4.1 (2.6-6.5)). In addition, previous use of other PPIs was documented in 31.2% of cases and 17.2% of controls.

For a subset of 33 non-responders and 33 matched responders additional information was gathered. 48.5% of these 66 patients were evaluated by specialists and 51.5% by GPs. The distribution of characteristics revealed no significant differences between cases and controls, the pattern was comparable with the pattern shown in Table 1. The distribution of indications for therapy was also quite similar among this subset of cases and controls. None of the 66 patients had a history of gastric surgery.

Regarding cases, treatment with PPIs during the preceding year was reported in 9 patients and resulted in a disappearance or improvement of acid related complaints in 4 patients, whereas in 5, acid related complaints remained equal. 6 control patients had used PPIs during the last year, resulting in a disappearance or improvement of acid related complaints in 5 patients, whereas in one patient the outcome was not known.

Previous use of H_2-receptor antagonists was reported by the physician in 3 cases and 5 controls. In all cases and 4 controls this resulted in an equalising of acid related complaints. In one control patient the complaints reduced.

Compliance, as assessed by the patient, did not differ between cases and controls. No intake for more than one day was reported by 9.1% of cases and 9.1% of control patients. Moreover, the intake of lansoprazole was not skipped or only occasionally skipped for a day by 90.9% of cases and 90.9% of control patients. In one case and two control patients the prescribed lansoprazole doses, as documented by the physician, differed from the information received from the patient.

DISCUSSION

The aim of this follow-up study was to investigate determinants of non-response to lansoprazole use in daily practice. In an initial observational study we found that indication-related complaints disappeared or improved in 90.5% of patients after 8 weeks of lansoprazole use [4]. In this study in daily clinical practice the response was recorded analogous to normal procedures, meaning that symptomatic or less frequently endoscopic diagnostic methods were practised. There were no significant differences in response to PPI therapy for the various indications. In clinical studies healing rates are nearly always assessed by endoscopy and in patients with e.g. GERD, gastric ulcers and NSAID-induced ulcers 8-week healing rates of respectively 75-92%, 94.4% and 95% are described [1, 11, 12]. Thus, the effectiveness of lansoprazole when used in daily practice was comparably high.

The likelihood that non-response was related to certain determinants was evaluated by the comparison of responding and non-responding patients in daily clinical practice. The study data were derived from a prospective, open label, observational follow-up study following 10,008 lansoprazole users. To diminish observer bias and to improve power, non-responding patients were matched with responding patients from the same physician in a ratio of 1:2.

Determinants such as gender, alcohol use, prescribed lansoprazole dose and co-morbidity were not associated with non-response. Although expected, no difference was detected regarding the indication of therapy. Unlabelled indications e.g. 'dyspepsia' or ‘gastritis’ (whether or not confirmed by endoscopy) showed no association with non-response. Psychiatric co-morbidity might affect compliance in a negative way and thus affect the response to lansoprazole [7]. Nevertheless we did not see such an association. Gastrointestinal co-morbidity was also not significantly associated with non-responding patients. If this had been the case, this might have been an indication of the presence of gastrointestinal disorders or gastrointestinal surgery affecting the PPI absorption or metabolism. We did find a significant association between non-response and heavy smoking. It is known that smoking has a role in the pathogenesis of duodenal ulcer disease and that relapse rates are higher in smokers [13, 14]. Also an age > 60 years showed to be significantly associated with non-response. Previous use of any PPI, as registered by the physician, was strongly associated with non-response (adjusted OR (95%

CI): 4.1 (2.6-6.5)). Higher previous use of PPIs in non-responding patients might suggest channelling or resistance to PPIs. The small subset revealed that, 5 out of 9 non-responding patients with previous use of PPIs during the preceding year also had an unsatisfactorily response on this previous PPI. Resistance in PPI users is rare, but ulcers can be resistant to PPI treatment due to an inadequate suppression of gastric acidity by reduced gastric emptying [3]. If adequate plasma levels are not achieved gastric acidity may be insufficiently inhibited; this will be more common with omeprazole than with lansoprazole due to different coatings [3].

Another factor that has an effect on the response is the patient compliance, in routine daily practice the control of compliance is especially low. It has been established that psychological factors (co-operation, comprehension of treatment schedule), the disease (acute or chronic, hospitalised or outpatient) and the treatment (frequency of intake, improvement of symptoms, side effects) influence practice where compliance is low [7, 15]. No differences were found regarding the compliance, as assessed by the patient, in the small subset. In case of doubt, gastrin levels can be assessed to evaluate the compliance.

In conclusion, this study was set up to investigate determinants related with the infrequent occurrence of therapeutic non-response to lansoprazole treatment in daily practice. Previous use of PPIs, an age above 60 years and a well known co-factor smoking were significantly associated with non-response, whereas unlabelled indications showed no relation with non-response to lansoprazole use in daily practice. Previous use of PPIs in non-responding patients might suggest resistance to PPIs [3]. The knowledge that non-response drives non-response may encourage physicians to follow PPI users with previous PPI use more closely.

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Chapter 3

Drivers of prescriptions for lansoprazole

Chapter 3.1

NSAID use is an important driver of starting lansoprazole treatment

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SUMMARY

Background: Use of NSAIDs is widespread. It is well known that NSAIDs may induce acid related disorders and that proton pump inhibitors (PPIs) are used to prevent and treat these complaints in NSAIDs users. We assessed the prevalence of PPI use associated with NSAIDs use in daily clinical practice. Furthermore, we investigated possible associated determinants and trends in time.
Methods: A prospective observational follow-up study of lansoprazole use in the Netherlands during the first four years after marketing from January 1994 until April 1998. The prevalence of the simultaneous start of lansoprazole and NSAID therapy and the use of lansoprazole following NSAID use were assessed as markers for preventive and possibly NSAID induced use.
Results: From 1994-1997, 8.4% - 19.4% of all lansoprazole users had a history of NSAID use, whereas in 1.6% - 2.2% of all lansoprazole users lansoprazole was started together with NSAID therapy. Concomitant use of corticosteroids and/or anticoagulants as well as female sex and an age between 45 and 75 were revealed to be associated factors for NSAID related lansoprazole use.
Conclusion: In 1997 up to one out of every five first prescriptions of lansoprazole treatment was related to NSAID use. Awareness of NSAID use is pertinent, since specific patient groups were identified with an increasing risk to develop acid related disorders.

INTRODUCTION

NSAID use is very common for a wide range of conditions including arthritis and musculoskeletal disorders; elderly people and females are especially prone to be chronic users [1]. It is well known that NSAIDs may induce acid related disorders through both a topical and a systemic effect with a prevalence of ulceration between 14 and 31% [2, 3]. In fact, NSAID and analgesic use accounts for two out of every three drug related hospitalizations [4]. Pharmacotherapy, including PPIs, H2 antagonists and misoprostol, may be used to prevent and treat these acid related disorders in NSAID users [5, 6].

The major impact of NSAIDs and the increasing use of drugs to treat acid-related disorders were the rationale to assess the prevalence of PPI use associated with NSAID use. Two types of NSAID-associated PPI use may be distinguished: preventive and NSAID-induced use. We performed a study in a large cohort of users of lansoprazole, a PPI, and investigated the number of patients with possibly preventive use, or NSAID-induced use. Furthermore, we analysed possible associated determinants (e.g. history of peptic ulcer, high age, smoking, male sex, indication, short term use, concomitant corticosteroid or anticoagulants use) and trends in time [3, 6-10].

MATERIALS AND METHODS

Design

A prospective observational follow-up study including all lansoprazole users by a sample of 1,071 physicians in The Netherlands during the first four years after marketing (January 1994 until April 1998) [11]. No inclusion or exclusion criteria were applied other than the use of lansoprazole.

Measurements

Participating physicians collected data including age, gender, smoking behaviour, primary indication of lansoprazole prescription, daily lansoprazole dose and past use of acid related drugs. No specific tests were requested from the physician with regard to the primary diagnosis. Complete medication histories of patients over six months before starting therapy and during follow-up were retrieved at

the local pharmacy and available for 6,868 patients in this study. Computerisation of pharmacy records, and thus the compilation of medication histories, is almost universal in the Netherlands [12]. The majority of patients (78%) are designated to a single pharmacy for all reimbursed prescription drugs. Drugs used were coded according to the Anatomical-Therapeutic-Chemical (ATC) classification [13].

Analysis

Preventive use of lansoprazole was defined as a simultaneous prescription of lansoprazole and a NSAID in patients with no history of acid related drug use during the previous six months. Possibly NSAID-induced lansoprazole use was defined as start of lansoprazole therapy in patients chronically using NSAIDs during the preceding 6 months. The population attributable risk (PAR) of NSAID-use was calculated through the method for case-control studies described by Coughlin [14]. Results were tabulated in absolute values and percentages. Baseline comparisons were calculated using χ^2-tests against non NSAID users.

RESULTS

As can be seen in Table 1, our data set included 6,868 patients with a lansoprazole prescription. Of these, 1,053 (15.3%) were associated with NSAID use. We found 135 (2.0%) patients with preventive lansoprazole prescriptions and 918 (13.4%) with possibly NSAID-induced lansoprazole prescriptions.

Table 1
NSAID related lansprazole use in 6,868 patients (1994-1997)

	1994 N (%)	1995 N (%)	1996 N (%)	1997 * N (%)	Total N (%)
Lansoprazole users	2,142	2,223	1,821	682	6,868
Possibly NSAID induced	180 (8.4)	265 (11.9)	341 (18.7)	132 (19.4)	918 (13.4)
NSAID prevention	48 (2.2)	32 (1.4)	44 (2.4)	11 (1.6)	135 (2.0)
Total NSAID related	228 (10.6)	297 (13.3)	384 (21.1)	144 (21.0)	1053 (15.3)

* Including patients included from January until April 1998

A clear trend in time was visible with an increase of all NSAID related lansoprazole prescriptions from 10.6% in 1994 up to 21.0% in 1997. The percentage of possibly NSAID-induced lanzoprazole prescriptions increased in this period from 8.4% to 19.4%, whereas preventive lansoprazole use remained around 2.0% of all lansoprazole prescriptions during these four years.

Table 2
Determinants associated with (non-)NSAID use

	Non NSAID use N=5,815 (%)	Preventive lansoprazole use N=135 (%)	NSAID induced lansoprazole use N=918 (%)
Female	2,957 (50.9)	84 (62.2)*	566 (61.7)**
Age			
0-45	1,653 (28.4)	35 (25.9)	225 (24.5)
45-60	1,925 (33.1)	44 (32.6)	318 (34.6)*
60-75	1,615 (27.8)	37 (27.4)	270 (29.4)*
> 75	622 (10.7)	19 (14.1)	105 (11.4)
Smoking	1,571 (27.0)	30 (22.2)	245 (26.7)
Specialist	2,023 (34.8)	33 (24.4)*	344 (37.5)
Past use			
H_2-receptor antagonist	2,556 (44.0)	55 (40.7)	388 (42.3)
PPI	850 (14.6)	19 (14.1)	102 (11.1)**
Primary diagnosis			
Ulcer	945 (16.3)	24 (17.8)	139 (15.1)
GERD	3,301 (56.8)	77 (57.0)	504 (54.9)
Daily lansoprazole dose			
≤ 30 mg	5,521 (94.9)	131 (97.0)	879 (95.8)
≥ 60 mg	294 (5.1)	4 (3.0)	39 (4.2)
Concomitant use of medication			
Corticosteroids	114 (2.0)	6 (4.4)*	72 (7.8)**
Anticoagulants	336 (5.8)	7 (5.2)	97 (10.6)**

* $p<0.05$

** $p<0.01$

We assumed a prevalence of 3% of NSAID use in the general population [1, 3, 15]. This leads to estimation of an odds ratio for use of NSAIDs in patients starting lansoprazole therapy of 5.0, resulting in a population attributed risk (PAR) of 10.7%. This means that 10.7% of all lansoprazole prescriptions could be attributed to previous use of NSAIDs.

Other determinants possibly related to NSAID-associated lansoprazole use were investigated and results are shown in Table 2. Smoking behaviour, past use of H2-antagonists, primary diagnosis and daily lansoprazole dose were not significantly associated with any of the lansoprazole prescriptions. Female sex showed to be associated with preventive use of lansoprazole in NSAID users ($p<0.05$) as well as with possibly NSAID induced lansoprazole use ($p<0.01$). Age between 45 and 75 years was related with possibly NSAID-induced lansoprazole use ($p<0.05$). Preventive lansoprazole therapy was significantly less frequently prescribed by specialists compared to general practitioners ($p< 0.05$). Past PPI use was significantly less frequent in patients with possibly NSAID-induced lansoprazole use compared to non NSAID users ($p<0.001$). Concomitant use of corticosteroids showed a strong association with preventive lansoprazole use ($p<0.05$) and an even stronger relation with NSAID-induced use ($p<0.01$). In addition, anticoagulants as co-medication were significantly more frequently prescribed for patients with NSAID induced lansoprazole prescriptions ($p<0.01$).

DISCUSSION

NSAID and PPI use is widespread [1, 16]. This was the rationale to assess the prevalence and possible associated determinants of lansoprazole use associated with NSAID use in daily clinical practice. We found that in 1997 one out of five lansoprazole prescriptions was NSAID related. In British general practices, 17% of the patients on long term acid suppressing treatment were also using NSAIDs, with or without prescription [16].

Overall during the total study period, 13.4% of all lansoprazole prescriptions were possibly induced by NSAID use, whereas in 2.0% lansoprazole was preventively prescribed. The population attributed risk (PAR) was 10.7%, meaning that 10.7% of all lansoprazole prescriptions can be attributed to previous use of NSAIDs.

NSAIDs related preventive and therapeutic lansoprazole use was associated with concomitant use of corticosteroids, in accordance with previous investigations [3, 9]. Moreover, concomitant use of anticoagulants, female sex and an age between 45 and 75 were associated with possibly NSAID-induced lansoprazole use, whereas previous PPI use showed a negative association. Awareness of the increasing risk to develop acid related disorders during NSAID use is pertinent. The introduction of a new class of NSAIDs, the cyclooxygenase-2 enzyme inhibitors, with reduced risks of upper gastrointestinal ulceration or gastrointestinal adverse events may be an improvement in the treatment for conditions such as arthritis [17].

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Chapter 3.2

Does seeding drive prescription? Selection bias in a company sponsored postmarketing surveillance study

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Submitted for publication

SUMMARY

Background: There have been many concerns about industry bias and lack of scientific justification related to industry sponsored postmarketing cohort studies. We analysed whether a sponsored postmarketing study with a proton pump inhibitor (PPI) resulted in excess prescriptions in participating physicians and whether patients in such a study reflect the profiles of lansoprazole recipients in daily clinical practice.
Methods: We performed a prospective, observational study in which 10,008 lansoprazole users were followed over time marketing from January 1994 until April 1998. Basic characteristics of prescribers and patients of this study were weighed against observational data of the same period of the PHARMO database representing a general Dutch population.
Results: Results indicated that we followed 12.8% of all new Dutch lansoprazole users in our study. The patient characteristics of our population were fairly similar with those of the reference PPI users, regarding age, gender, prescriber and prescription patterns. Previous PPI use was less frequently reported in our study as compared with the reference group. Nevertheless, the pattern in time and the relation with the type of prescriber were comparable between the postmarketing study and the reference PPI users.
Conclusion: We followed over one out of every eight new Dutch lansoprazole users in time. With the exception of previous PPI use, we established that the prescribers and patients in our study were comparable with the reference patients. This could indicate a selection of relatively non-complicated patients in the postmarketing study. Furthermore, we found no indicators that the postmarketing study drove prescriptions in participating physicians.

INTRODUCTION

Selection of physicians and patients participating in a postmarketing surveillance or pharmacoepidemiological study may bias the outcome of such a study [1-5]. In 1992 an important analysis was published on industry sponsored post-marketing studies [6]. It was concluded that postmarketing surveillance studies were not always correctly designed and encountered problems with enrolment, leading to only a limited contribution to the assessment of drug safety. On the other hand, there is a continuous necessity to rationale the effectiveness and safety of medicines when used in daily clinical practice after marketing, since safety is a significant drug therapy outcome [7, 8]. Drug related problems are probably one of the most frequently occurring and important health risks [9]. According to Wood et al, active postmarketing should be routinely performed and mandatory when there is a priori reason to suspect that a drug may have adverse events [10, 11]. This is illustrated by Bennett et al in their investigation of the adverse event thrombotic thrombocytopenic purpura associated with clopidogrel, which was an adverse event previously reported with ticlopidine, a drug with a similar mechanism of action and chemical structure [12].

How can the outcome of a postmarketing study become biased? Selection of physicians may influence the patient population, the choice of drugs prescribed, and the outcome measures of the study [13]. Selection of patients may influence the generalisation of the study through differences in demographic characteristics, medical history, co-morbidity and co-medication, disease severity or baseline risk and compliance compared with a normal patient population. The strength of pharmacoepidemiological research into newly marketed drugs lies in its observational nature and thus can add to evidence from (pre-registration) clinical research, which is often conducted with selected and skewed populations [13]. Although observational research is by definition non-interventional, additional action is often required from participating physicians and sometimes patients, especially in the prospective follow-up design that most postmarketing studies use in which inclusion and follow-up is performed through questionnaires [1]. This leads to an extra workload for the physicians and a burden to the patients, resulting in refusal to participate. Other reasons not to participate in studies are reluctance to prescribe new drugs, disapproval of industry-sponsored studies in general or lack of knowledge of pharmacoepidemiological research.

However, if physicians are remunerated for their involvement in a study, this may lead to more enthusiasm to contribute or even drive prescriptions [1]. The right balance between scientific work, involvement of physicians and patients and promotional activities has to be discovered for every postmarketing study. Even though the SAMM guidelines provide a valuable format for finding the right equilibrium, postmarketing practice shows various cases of studies leading to discussion [14, 15].

We performed a large scale postmarketing study into the effects and usage patterns of lansoprazole, a PPI introduced on the Dutch market at the end of 1993 and at that time registered for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers [16]. In this study a total of 10,008 users of lansoprazole were followed by general practitioners (GPs) and specialists during the first four years after introduction on the Dutch market. We analysed whether a sponsored postmarketing study resulted in excess prescriptions in participating physicians and whether patients in such a study reflect the profiles of lansoprazole recipients in daily clinical practice.

MATERIALS AND METHODS

Design

The prospective, observational follow-up study was carried out in 10,008 lansoprazole users in the Netherlands during the first four years after marketing from January 1994 until April 1998 [16]. No inclusion or exclusion criteria were applied other than the use of lansoprazole. The study design was aimed at a population as representative as possible of the population of lansoprazole recipients with a clear separation in time between the prescribing of lansoprazole and the inclusion of the patient in the study in order to minimise the influence of the study on prescribing behaviour and evaluation, following SAMM guidelines [6]. The overall design has been described in detail elsewhere [16].

Patients

All patients being prescribed lansoprazole were included in the postmarketing study at the first visit or any later follow-up visit after lansoprazole was prescribed. Patients agreed to participate by giving their free informed consent al-

lowing access to all relevant clinical and medication data and storage and analyses of these data. To maintain patient anonymity patients were identified by an identification code only.

No further selection criteria were used, meaning that every lansoprazole user independent of diagnosis (labelled or unlabelled, diagnostically tested or not) could enter the study.

The comparison data were collected from PHARMO, a Dutch database of complete medication histories of a population of 450,000 persons [17]. These data were routinely gathered from automated pharmacy records and contain information on all prescription medication from GPs and specialists for non-institutionalised patients. These data can be generalised to the Dutch population. All new patients with at least one new prescription for lansoprazole during the years 1994-1997 were selected (N=2,087). A new patient was defined as having at least a period of 6 months before start with no prescription for lansoprazole.

Analysis

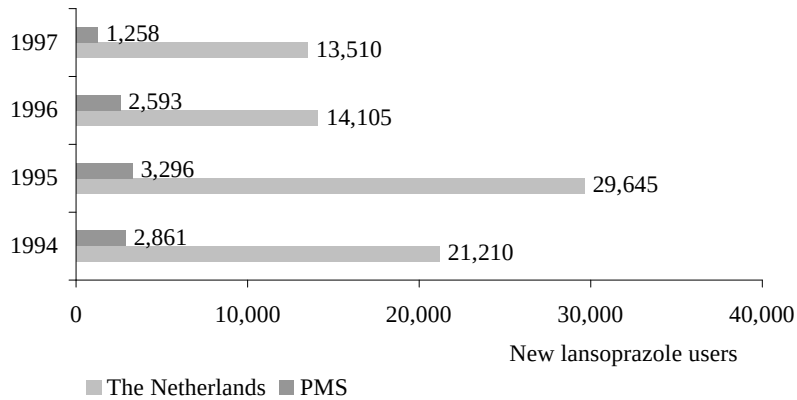
Characteristics of patients including age, gender, prescriber and previous antiulcer or *Helicobacter pylori* (*H. pylori)* eradication therapy, as well as features of prescribers during four consecutive years including the incidence density of new lansoprazole prescriptions were compared for the two samples.

Baseline comparisons were calculated using crude rate ratios with a confidence interval of 95%. Statistical significance was defined at p-value < 0.05. Results were tabulated in absolute values and percentages. All statistical analyses were performed using the SAS statistical package.

RESULTS

In Figure 1, the number of new patients is given for our postmarketing study (PMS) compared to The Netherlands (PHARMO data standardised to the Dutch population). Overall, 12.8% of all Dutch patients with new lansoprazole prescriptions were included in our study. This figure ranged from 13.5%, 11.1%. 18.4% to 9.3% for each consecutive year starting from 1994. In 1996 nearly one out of every five Dutch lansoprazole users was included in our study.

Figure 1
Number of new lansoprazole users in the Netherlands (N=78,740) and the postmarketing study (N=10,008)



In Table 1, patient characteristics of lansoprazole users were compared between patients included in the postmarketing study and patients captured by the PHARMO Record Linkage System [17]. We included a smaller number of women (51.4%) in our study as compared to the reference patients (55.7%); the difference was not significant (OR (95% CI): 0.8 (0.8-1.0). Our reported age distributions of men and women were comparable with results of the reference patients for all age categories.

Every GP and specialist in The Netherlands was invited to participate in the postmarketing study. In total 266 specialists and 805 GPs participated. We found that 61.6% of the prescriptions of our study came from GPs, whereas GPs accounted for 68.4% of the new PPI prescriptions of the reference patients (OR (95% CI): 0.7 (0.7-0.8)).

If we compare figures from before 1996 versus after 1996 we noted that GPs of the reference patients accounted for successively 68.5% and 68.1% of the prescriptions, whereas GPs of the postmarketing study accounted for consecutively 60.5% and 63.0% of the prescriptions. After 1996, the difference was not statistically significant with an OR (95% CI) of 0.8 (0.7-1.0).

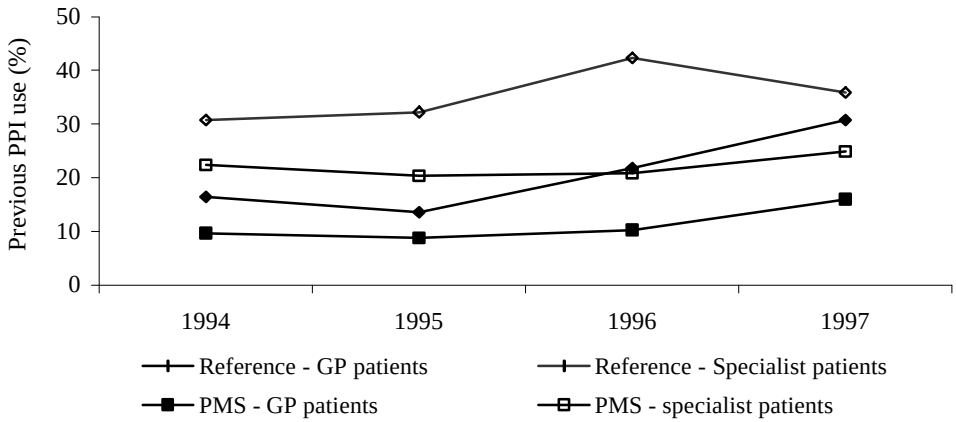
Table 1
Distribution of characteristics of reference patients and postmarketing study

	Reference patients		Postmarketing study	
	N=2,087	%	N=10,008	%
Men	924	44.3	4,864	48.6
0-30 years	88	4.2	375	3.7
30-45 years	230	11.0	1,285	12.8
45-60 years	296	14.2	1,648	16.5
60 - 75 years	235	11.3	1,178	11.8
> 75 years	75	3.6	378	3.8
Women	1,163	55.7	5,144	51.4
0-30 years	87	4.2	284	2.8
30-45 years	229	11.0	911	9.1
45-60 years	358	17.2	1,631	16.3
60 - 75 years	342	16.4	1,590	15.9
> 75 years	147	7.0	728	7.3
GP	1,427	68.4	6,162	61.6
Previous anti-ulcer therapy				
PPI	479	23.0	1,478	14.8
H_2-receptor antagonist	1,159	55.5	4,275	42.8
Anti *H. pylori*	258	12.4	738	7.4
None of these	757	36.3	4,491	44.9

Previous use of PPIs was reported in 14.8% of our patients and in 23.0% of the reference patients (OR (95% CI): 0.6 (0.5-0.7)).

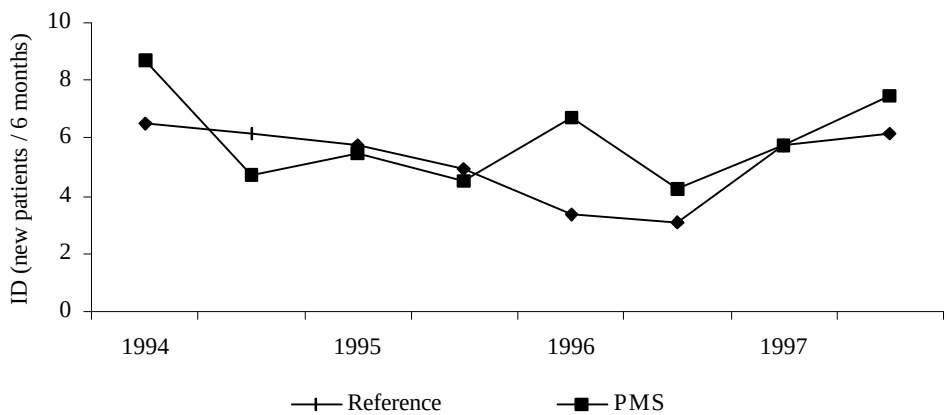
As depicted in Figure 2, we saw a small increase in time in the number of lansoprazole users with previous PPI use. This rise was more marked for the reference patients. Previous use of H_2-receptor antagonists and *H. pylori* eradication schedules were also more common in the patients captured by the reference patients (both OR (95% CI): 0.6 (0.5-0.7)). In addition, our patients had more often not used any of these three drug therapies in the past (OR (95% CI): 1.4 (1.3-1.6)).

Figure 2
Previous PPI use in time



In the PHARMO database, specialists can not be identified on an individual level. Therefore, we limited the analyses regarding incidence density of new lansoprazole prescriptions to GPs (Figure 3).

Figure 3
Incidence density (ID) of patients starting lansoprazole per GP



The incidence densities of new patients using lansoprazole remained fairly stable in time and were comparable for both samples of patients. The incidence densities were respectively 5.1 and 5.6 per 6 months for the reference group and our study. Overall during the four years, the GPs that participated in the postmarketing study included patients more frequently compared to new patients included by the reference group of GPs with an overall rate ratio of 1.09 (95% CI: 1.03 – 1.16). In the first 6 months of the study and during the first half of 1996, incidence density of new patients was considerably higher in the postmarketing surveillance group.

DISCUSSION

In this study we compared the sample of physicians and patients taking part in our postmarketing study with a sample of the general population in order to assess whether the postmarketing study resulted in more prescriptions by the participating physicians and whether selection had taken place. Selection may bias the outcomes and affect the generalisation of the results of pharmacoepidemiological research and is therefore an important subject of study.

We found that during the time frame of our study we included and followed 12.8% of all new lansoprazole users in the Netherlands: 10,008 users. These numbers depict that we indeed investigated a large sample of lansoprazole users. Patients from any age and gender category took part in our study, as in daily practice. This illustrates once more the additional value of postmarketing studies, because in clinical trials patients with low and high ages are excluded. In addition, it indicates that the physicians followed the protocol of the study, which emphasised that any patient with a new lansoprazole prescription be asked to participate, if willing to sign informed consent.

Our results demonstrate that characteristics of our population were comparable with the characteristics of the reference patients, with respect to age and gender. However, we found significantly lower numbers of lansoprazole users followed by GPs, compared with the reference patients. This may be caused by the fact that specialists usually are more motivated for prescribing and adopting newly marketed medicines compared to GPs and therefore also more willing to participate in clinical research [18-20]. In addition, we found that the difference between the postmarketing population and the reference group diminished in time

and became equal. Adoption of a new drug by physicians is highly variable and often erratic due to differences in prescribing attitudes, formulary policies, and marketing practices. Chan et al reported that dispensing of recently introduced NSAIDs achieved their equilibrium values in almost 2 years [21].

Previous use of PPIs was significantly less common in the postmarketing study compared to the reference patients, nevertheless the patterns of a slow increase in time of previous PPI use and the relation with the type of prescriber were identical for the reference patients and the postmarketing study. This could indicate a selection of relatively non-complex patients in the postmarketing study and thus represent that physicians were not eager to switch therapy for reason of the study.

The incidence densities of lansoprazole prescriptions by GPs were fairly similar in time among the reference patients and the postmarketing study. Although inviting physicians to participate may possibly influence prescribing, we only found a small difference. Expressed as a rate fraction we calculated that overall 9% of the patients included by the GPs in the study group, were caused by participation in the study. However, there appears to be a short-term effect of participation in these studies on the frequency in which new patients are included. During the first 6 months we saw that 25% of all patients included were because of participation in the study and a similar pattern was also seen in 1996, during which year extra marketing activity by the drug company was seen.

Furthermore, the detected differences may be partly explained by the different sources of data collection, pharmacy based versus observational follow-up. On the other hand, it is recognised that controlling for patient and prescriber variables does not diminish the extent of interpractititioner variability in prescribing rates, especially regarding new drugs [21, 22].

The reference group consisted of 2.6% of all new Dutch lansoprazole prescriptions (2,087/78,740), while our postmarketing study involved 12.4% of all new Dutch lansoprazole users (10,008/78,740).

In conclusion, we found no indicators for a substantial excess of lansoprazole prescriptions in physicians participating in the postmarketing study. Previous use of PPIs was significantly less common in the postmarketing study, which could indicate a selection of relatively non-complex patients. Furthermore, we found

that the prescribers and patients in our study were to a large extent comparable with the patients captured by the reference patients, regarding age, gender, prescriber and prescription patterns. Thus we could not confirm seeding bias in our postmarketing study. We did see that previous use of PPIs was less frequent in our study, but the pattern in time and the relation with the type of prescriber were identical for the reference patients and the postmarketing study.

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Chapter 4

Helicobacter pylori eradication therapy analyses

Chapter 4.1

Medley of *Helicobacter pylori* eradication regimens Combinations using lansoprazole

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SUMMARY

Background: The eradication of *Helicobacter pylori (H. pylori)* has become an important strategy in the treatment of GI disorders. In this study *H. pylori* eradication strategies during a four-year period in a group of patients treated with lansoprazole were explored and the use of pre- and post testing methods and their association with eradication strategy and success was assessed.
Methods: In a follow-up study 527 patients treated with lansoprazole as part of *H. pylori* eradication therapy were evaluated from 1994 up to 1998.
Results: According to Dutch and European recommendations developed in 1996-1997, 70 to 75% of the patients had an indication justifying *H. pylori* eradication. In total, in 83.9% of all patients a diagnostic test(s) was used prior to treatment. In total 22 different drug schedules were used. The triple combinations lansoprazole, clarithromycin and amoxicillin or metronidazole were used most commonly (in 33.6% and 18.4% of all patients respectively). In 28.3% (149/527) eradication was assessed and in 86.6% (129/149) of these patients *H. pylori* eradication was accomplished. Adverse events were reported in 19.4% of all patients. During the study there was a shift from prescribed dual to (specific) triple schedules, whereas quadruple schedules showed a small increase in use up to 20-30%. Specialists more often made use of specific methods for diagnosing compared with general practitioners (GPs).
Conclusions: Regarding the indications of use, the physicians practised in about 70-75% according to the guidelines. The recommended triple schedules were used in two out of three patients, but many other schedules were also prescribed. Pre-treatment diagnostic tests were very often performed; the frequency and pattern of testing did not change over time. Eradication rates were high and comparable with results from clinical trials. Nevertheless, post-treatment testing was frequent.

INTRODUCTION

Up to 50% of the world's population is infected with the bacterial pathogen *Helicobacter pylori*, the majority without symptoms. The infection is usually acquired during childhood or early adulthood. The pathogen was first cultured in 1982 and since then has become an important target in the treatment of peptic ulcer disease [1]. *H. pylori* is the main cause of gastritis and peptic ulcers (inducing 95% of the duodenal ulcers and 80% of the gastric ulcers) and is even a risk factor for gastric cancer, as three out of four gastric cancers may be attributable to the infection [2]. Recent evidence suggested that *H. pylori* is also associated with coronary heart disease, but this association is still under investigation [3, 4]. Considering the complications of *H. pylori* infection (15% of those infected will become seriously ill), eradication of *H. pylori* is the main strategy in treatment of gastritis and peptic ulcers [2]. Lansoprazole is a PPI introduced in the early 90s and indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers. Furthermore, lansoprazole is used in combination with antibiotics, bismuth subcitrate and/or metronidazole in the treatment of *H. pylori* infections [5]. In many comparative and non-comparative clinical trials PPIs have been examined in *H. pylori* eradication regimens [6]. Dual therapy was found to effectively eradicate *H. pylori infection in* 48-55% of cases; triple drug schedules showed eradication rates of 68-82% and quadruple schedules eradicated *H. pylori* in > 90-95% of infected patients [5, 6]. It has been shown that eradication reduces recurrence or relapse of ulcers [5, 7, 8]. A daily dose of 60 mg of lansoprazole as part of an eradication scheme has shown better results than a daily dose of 30 mg [5].

Besides effectiveness, safety and cost estimations have to be taken into account in the treatment of *H. pylori* infections. Adverse events, although mostly mild, are common during eradication therapies (18% during dual therapy and 33% during triple therapy) [6, 9-11]. In patients with chronic duodenal ulcer, *H. pylori* eradication reduces the use of long-term acid-suppression and/or ulcer-related health care resources, while the eradication of *H. pylori* in non-ulcer dyspeptic patients is controversial [12-16].

Another important issue is the discussion whether the indication to eradicate should be based on an assessment of symptoms or on a pre-treatment test [17]. Subsequently, the question arises whether or not success of eradication should be

verified by a post-treatment test. There are a number of methods used to confirm *H. pylori* infection and to assess eradication rates. The urease testing, histology and culture require an endoscopy. Non-invasive methods to diagnose *H. pylori* include urea breath testing and serology [18]. Recently, several European countries have adopted guidelines on the treatment of *H. pylori*. The development of these guidelines was prompted by the immense choice of drug schedules to eradicate *H. pylori* and the increasing number of available methods to test *H. pylori* infection. However, little data is available on the actual practice by physicians in *H. pylori* eradication [19, 20].

The goal of our study was to explore *H. pylori* eradication strategies during a four-year period in a group of patients treated with lansoprazole. Furthermore, we investigated the use of pre- and post testing methods and their association with eradication strategy and success.

MATERIALS AND METHODS

Design and patient selection

A large prospective observational follow-up study investigating safety, efficacy and patterns of use in 10,008 lansoprazole users was set up in daily clinical practice of GPs and specialists. The study protocol was designed according to the SAMM guidelines (guidelines for company-sponsored Safety Assessment of Marketed Medicines) on design of postmarketing safety studies and approved by the Medical Ethics Committee of the Utrecht University Medical Centre [21]. The study data were collected in the Netherlands between January 1994 and April 1998, these being the first four years after introduction of the drug on the Dutch market [21]. All patients gave their free informed consent in writing. No additional in- or exclusion criteria were considered. Of all 10,008 studied lansoprazole users, 527 were treated with dual, triple or quadruple *H. pylori* eradication therapies as confirmed by their physician and further investigated in this study.

Measurements

Baseline patient characteristics including age, gender, smoking habits, alcohol intake and co-morbidity were measured at the start of lansoprazole treatment.

Moreover, information was obtained on the primary indication for use of lansoprazole prescription and whether or not PPI therapy was part of *H. pylori* eradication therapy. Three different primary diagnoses were distinguished: peptic ulcer, gastro-oesophageal reflux disease and other diagnoses (e.g. 'gastritis', 'duodenitis'). No additional diagnostic tests were requested from the physician with regard to the primary diagnosis. The methods used to assess *H. pylori* diagnosis and eradication were recorded, including endoscopy (urease test, culture or histology), urea breath test and serology. Individual *H. pylori* eradication schedules were classified as dual (lansoprazole and antibiotic), triple (lansoprazole in combination with antibiotic(s), bismuth subcitrate and/or metronidazole) or quadruple (lansoprazole in combination with antibiotic(s), bismuth subcitrate and/or metronidazole) based on the number of different drugs included. Besides the prescribed drug schedules, the daily dose, duration and starting dates were collected. Compliance of drug intake was assessed by the physician as good (intake of over 80%), moderate (intake between 50 and 80%) and poor (intake of less then 50%) as well as completion of the course of treatment. Furthermore, the physician documented whether eradication was tested and achieved. No specific test to assess eradication was requested from the physicians. The physician recorded any past use of PPIs or H_2-receptor antagonists. This information was also collected from automated pharmacy records.

Analysis

Results were tabulated in absolute values and percentages. Baseline comparisons were calculated using crude odds ratios with a confidence interval of 95%. Statistical significance was determined through χ^2 tests and defined at $p<0.05$. All statistical analyses were performed using SAS and EGRET statistical packages.

RESULTS

Over a period of four years data were obtained from 527 lansoprazole users treated with *H. pylori* eradication therapies. Baseline characteristics of the patients are depicted in Table 1. The majority of the 527 patients were male (59.4%). The age distribution was as follows: 32.0% < 45 years, 35.3% between 45 and 60 years and the remaining 32.7% > 60 years old. Smoking was reported in 36.2% of the patients and alcohol use in 44.8% of the patients. The prescribed

daily dose of lansoprazole was most frequently 30 mg (75.1%) or 60 mg (22.6%), while in a minority of 2.3% of the patients 15 mg was prescribed.

Table 1
General characteristics of patients with *H. pylori* eradication therapy

	N=527	%
Women	214	40.6
Age (years)		
0-30	169	32.1
45-60	186	35.3
> 60	172	32.6
No smoking	336	63.8
Smoking < 15 units/day	133	25.2
Smoking ≥ 15 units/day	58	11.0
No Alcohol consumption	291	55.2
Alcohol consumption < 5 units/day	225	42.7
Alcohol consumption ≥ 5 units/day	11	2.1
Daily dose of lansoprazole		
15 mg	12	2.3
30 mg	396	75.1
60 mg	119	22.6
Specialist	360	68.3
Previous use of acid reducing drugs		
Proton pump inhibitor	78	14.8
H_2-receptor antagonist	277	52.6
None of both	207	39.3
Primary Diagnosis		
Ulcer (without GERD)	209	39.7
GERD (without ulcer)	74	14.0
Ulcer and GERD	22	4.2
Other	222	42.1

Table 1
(continued) General characteristics of patients with *H. pylori* eradication therapy

	N=527	%
Method of *H. pylori* diagnosis		
Any specific method	442	83.9
Endoscopic: urease test	212	40.2
Endoscopic: culture	69	13.1
Endoscopis: histology	200	38.0
urea breath test	3	0.6
Serology	42	8.0
Other not specific method	84	15.9
Unknown	1	0.2
Co-morbidity present at inclusion		
None	398	75.5
Other gastrointestinal	38	7.2
Cardiovascular	46	8.7
Endocrine	29	5.5
Respiratory	13	2.5
Musculoskeletal	12	2.3
Psychiatric	9	1.7

In total 60 specialists evaluated 68.3% of the patients, 91 GPs evaluated the remaining patients. Of all patients 52.6% had used H_2-receptor antagonists and 14.8% PPIs in the past, whereas 39.3% had used neither of these acid reducing drugs. Co-morbidity at the start of the lansoprazole therapy was only present in 24.6% of the patients and mainly included cardiovascular (8.7%), other gastrointestinal (7.2%) or endocrine diseases (5.5%).

The primary diagnosis of patients treated with an eradication therapy was most frequently peptic ulcer without gastro-oesophageal reflux disease (39.7%), in 14.0% oesophageal reflux disease without peptic ulcer and in 4.2% peptic ulcer with gastro-oesophageal reflux disease. In 42.1% the primary diagnosis was any other diagnosis such as ‘gastritis’ or ‘dyspepsia’.

In total 83.9% of all patients were tested for *H pylori* pre-treatment by histology, culture, urease test, serology and/or breath test, while in the remaining 15.9% of the patients a non specific method was claimed to have been used to confirm the diagnosis including medical history or presented symptoms. Specialists (92.2%) more often performed specific tests compared to GPs (65.9%). Peptic ulcer patients were less frequently tested with a specific method (75.3%) compared to patients with other primary diagnosis (90.5%). In general, the most frequently performed specific methods were urease test (40.2%), histology (38.0%) and culture (13.1%). Serology and breath tests were conducted in 8.0% and 0.6% respectively.

According to the Dutch recommendations, 70.0% of our patients had an indication justifying *H. pylori* eradication (i.e. gastric ulcer or 'gastritis' both endoscopically confirmed and specifically tested for *H. pylori*, or endoscopically confirmed duodenal ulcer) [19]. Following the definitions of the European consensus, 74.6% of our patients had a proper indication for *H. pylori* eradication; namely peptic ulcer, 'gastritis' or 'dyspepsia' all specifically tested for *H. pylori* [20].

As can be seen in Table 2, in total 22 different combinations of drugs were prescribed for the eradication of *H. pylori*, namely 4 dual, 11 triple and 7 quadruple schedules. Triple therapy was most commonly prescribed (64.7%), followed by quadruple therapy (23.3%) and least commonly dual therapy (12.0%). If type and dose of antimicrobials and duration of therapy are taken into account over 67 regimens were used. With respect to quadruple schedules, 99.2% of these patients were treated for 4 days or more, while in one patient the duration of use was unknown. Regarding triple schedules, the duration of therapy was 7 days or more in 96.8%, less then 7 days in 0.3% and in the remaining patients (2.9%) the duration was unknown. Duration of use for dual schedules was 14 days or more in 54.0% and less then 14 days in 46.0%.

Of the four dual schedules, the most frequently used was lansoprazole in combination with amoxicillin seen in 8.5% of the patients (45/527). Amoxicillin in a daily dose of 2000 mg was used in a majority of these patients (34/45), whereas the minimum and maximum prescribed daily doses were respectively 1000 and 3000 mg. Other dual therapies were prescribed infrequently and were combinations of lansoprazole with clarithromycin, tetracyclin or roxythromycin.

Table 2
Drug regimens for the eradication of *H. pylori*

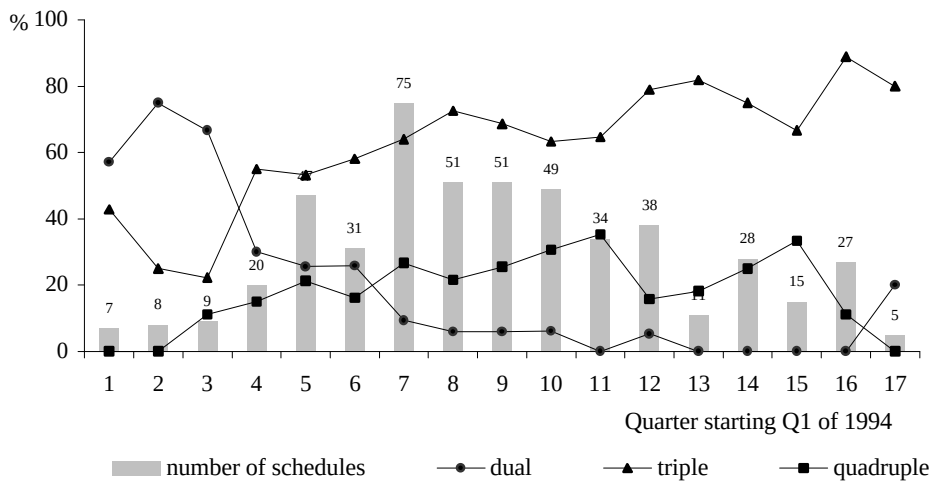
	N=527	%
Dual therapy of lansoprazole with:	63	12.0
Amoxicillin	45	8.5
Clarithomycin	14	2.7
Tetracyclin	2	0.4
Roxythromycin	2	0.4
Triple therapy of lansoprazole with:	341	64.7
Clarithomycin + amoxicillin	177	33.6
Clarithomycin + metronidazole	97	18.4
Tetracylcin + metronidazole	21	4.0
Amoxicillin + metronidazole	21	4.0
Clarithomycin + tinidazol	12	2.3
Amoxicillin + roxithromycin	5	0.9
Amoxicillin + bismuth subcitrate	3	0.6
Metronidazole + bismuth subcitrate	2	0.4
Clarithomycin + tetracyclin	1	0.2
Clarithomycin + bismuth subcitrate	1	0.2
Augmentin + metronidazole	1	0.2
Quadruple therapy of lansoprazole with:	123	23.3
Tetracyclin + bismuth subcitrate + metronidazole	100	19.0
Clarithomycin + bismuth subcitrate + tinidazole	9	1.7
Amoxicillin + bismuth subcitrate + metronidazole	7	1.3
Clarithomycin + bismuth subcitrate + metronidazole	3	0.6
Amoxicillin + clarithomycin + bismuth subcitrate	2	0.4
Amoxicillin + clarithomycin + metronidazole	1	0.2
Clarithomycin + bismuth subcitrate + augmentin	1	0.2

Regarding the 11 different triple therapies, the combination clarithromycin and amoxicillin was used in 33.6% of all patients (177/527), mainly in daily doses of 1000 mg clarithromycin with 2000 mg amoxicillin (141/177). Another frequently prescribed triple therapy was the combination lansoprazole, clarithromycin with metronidazole seen in 18.4% of the patients (97/527). This combination was used

in 5 different dosage forms, of which metronidazole 1000 mg and clarithromycin 1000 mg was prescribed in 58 of the 97 patients and metronidazole 1000 mg and clarithromycin 500 mg in 29 of the 97 patients. Other triple therapy schedules with lansoprazole included metronidazole and tetracyclin (21/527 all daily doses of 1000 mg), metronidazole and amoxicillin (21/527 in 11 different doses) and other regimens (25/527). Of the 7 quadruple schedules with lansoprazole the combination with tetracyclin, metronidazole and bismuth subcitrate was the most frequently prescribed in 19.0% (100/527). A daily dosage of 2000 mg tetracyclin, 1500 mg metronidazole and 480 mg bismuth subcitrate was the most popular combination (66/100).

Adverse events were reported in 19.4% of all patients. Most patients experienced one (10.6%) or two (5.5%) adverse events. The most frequently reported adverse events were mild in nature and included diarrhoea (4.9%), symptoms/complaints of mouth/tongue/lip (4.4%), nausea (4.0%), headache (2.7%) and dizziness (2.3%).

Figure 1
Prescribed Helicobacter pylori schedules (n=506) for subsequent quarters: total number and percentages for dual, triple and quadruple schedules

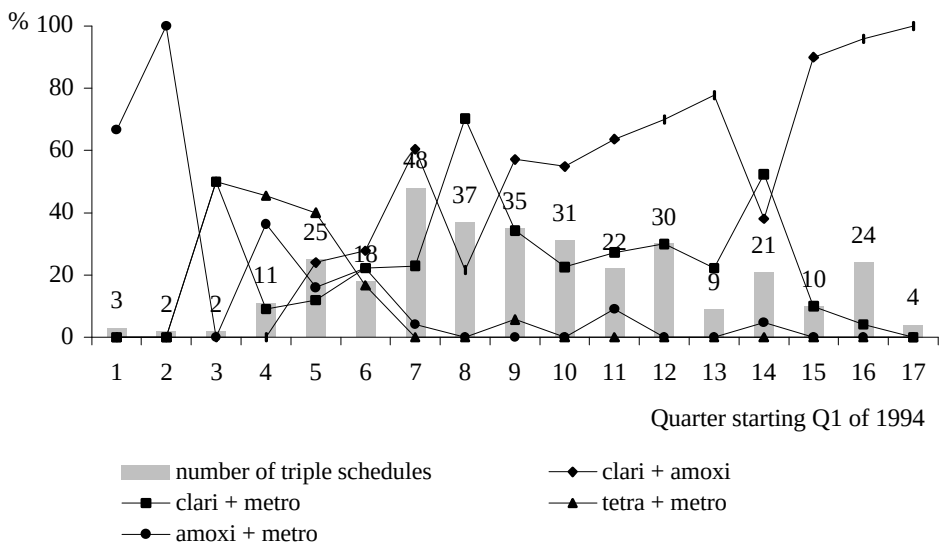


In Figure 1 the starting dates of the prescribed schedules are depicted per subsequent quarter in time for a total of four years starting quarter one of 1994. In 1994 eradication therapy was infrequent.

It can be seen that dual schedules were the most frequently used schedules in the first two years and thereafter the most infrequently prescribed regimens. The use of triple schedules increased from just above 20% to over 80% of all treatments and was the most prevalent prescribed treatment. Quadruple schedules were prescribed in less then 20% of the regimens prescribed in 1994, this increased to 30% in later years. These patterns were similar for patients evaluated by GPs and specialists, although increases and decreases appear to have occurred approximately six months earlier in specialists compared to GPs.

Looking in more detail at the prescribed triple schedules (Figure 2) we saw the first use of triple schedules slowly starting at the end of 1994. During 1994 and

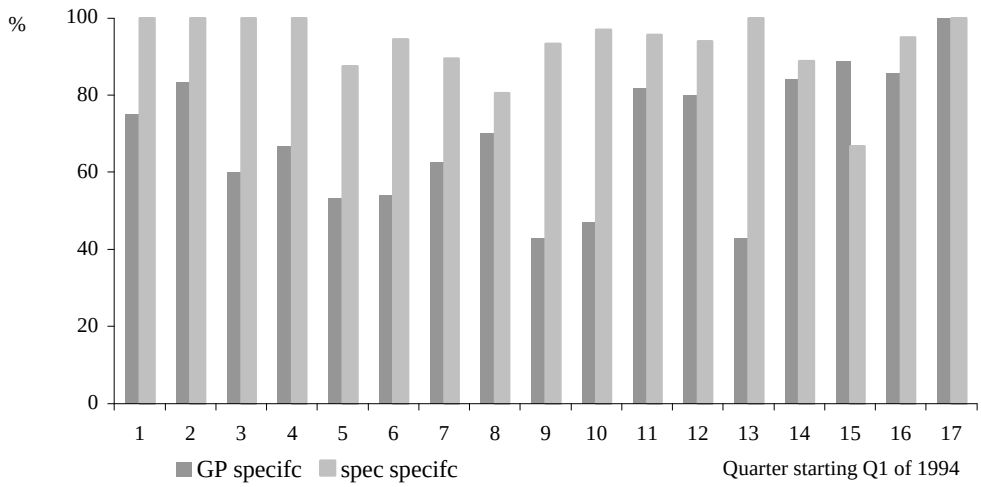
Figure 2
Pattern in time of most frequenltly prescribed triple schedules (n=308 of 332) per quarter



1995 the combinations of lansoprazole with either amoxicillin and metronidazole or tetracyclin with metronidazole were the most commonly prescribed schedules.

Hereafter these schedules were rarely used. In mid 1995 the first use of a combination of lansoprazole, clarithromycin and amoxicillin was reported, this became increasingly used in the following years due to the expense of the combination of lansoprazole, clarithromycin with metronidazole. The results of spring 1997 (quarter 14) were not consistent with the surrounding quarters, but might be explained by the fact that 10 of the 11 lansoprazole, clarithromycin and metronidazole combinations where prescribed by no more than two physicians.

Figure 3
Use of specific and aspecific tests to diagnose Helicobacter pylori by GPs (n=161) versus medical specialists (n=345) for subsequent quarters



We found no clear time trend for the different methods used to diagnose *H. pylori*. As can be seen in Figure 3, specialists used specific methods, such as histology, culture, urease test, serology and/or breath test in 80% to 100% of their patients and GPs in 60% to 80%. Urease test and histology were the most popular

used specific methods especially by specialists, followed by culture where a small difference was seen between specialists and GPs. In general, breath test and serology were very infrequently used as a method to diagnose *H. pylori*. No trends in time were seen for the breath test, culture, histology or urease test, while GPs more frequently reported serological tests in the last year of the study in 1997.

Post-treatment testing may be a sign for continued complaints. In the group of 442 (83.9%) patients with a pre-treatment specific diagnostic test, we looked at determinants associated with post-treatment testing. Post-treatment testing occurred in 154 of the 442 patients. We found that previous PPI use (20.1% versus 11.1%; OR (95% CI): 2.0 (1.1-3.6)), a 60 mg daily dose of lansoprazole (29.2% versus 16.7% OR (95% CI): 2.1 (1.3-3.4)) and use of a quadruple schedule (30.5% versus 20.5% OR (95% CI): 1.7 (1.1-2.7)) were determinants associated with post-treatment testing.

149 patients (28.3%) had both a pre-treatment test on H. *pylori* infection and a post-treatment test on the success of eradication. In these patients endoscopy was the most commonly used method to assess eradication (87.2%) compared to serology alone and/or breath testing (12.8%). The patients were treated with dual schedules in 8.7% of cases, triple schedules in 60.4% of cases and quadruple schedules in 30.9% of cases. Eradication was achieved in 86.6% (129/149). Eradication rates for dual, triple and quadruple schedules were 69.2% (9/13), 84.4% (76/90) and 95.7% (44/46) respectively.

DISCUSSION

The primary objective of this study was to investigate *H. pylori* eradication strategies in naturally occurring lansoprazole users. Over a period of four years we obtained data from 527 lansoprazole users treated with some kind of *H. pylori* eradication therapy. In our study, *H. pylori* eradication was far more frequently attempted by specialists (68.3%) compared to GPs (31.6%). This seems to be consistent with normal clinical practice during the study period (1994 –1998). In the US in 1994, nearly all (99%) gastro-enterologists prescribed *H. pylori* eradication therapy, compared to only two thirds of the GPs [22]. The Danish surveillance found a surprisingly extensive use in general practice, where GPs prescribed 62% of all eradication therapies and specialists 27%. According to the

authors, this pattern might be an indication that *H. pylori* eradication is not properly targeted [23].

In a majority of our patients (70%) the indication for *H pylori* eradication reflected the recently introduced Dutch guidelines [19, 20]. This finding is particularly interesting since the terms 'gastritis' and 'dyspepsia' were not further specified as. 'haemorraghic gastritis' and 'functional dyspepsia' for example in our study and that our data were predominantly collected before the introduction of the guidelines. Other studies also indicate that the majority of general practices act in accordance with current recommendations [24].

As many as 83.9% (442/527) of patients were specifically tested for *H. pylori* pre-treatment. In peptic ulcer patients this percentage was lower (75.4%) compared to patients with other primary diagnoses (90.5%), reflecting the Dutch recommendations. Cost estimates and reimbursement issues need to be taken into account. This implies that GPs especially will have problems with whom to test for *H. pylori* and whom to treat [25]. Dutch guidelines recommend performing culture, histology or urease testing to diagnose *H. pylori*, however all of these methods necessitate endoscopy. In our study *H. pylori* was diagnosed in 75.9% of the patients by such a method. This is high compared to results of a study in general practice in Scotland where *H. pylori* diagnosing was performed in only one third of patients [26]. No clear changes in the different tests used from 1994 up to 1998 were seen. In a substantial amount of the patients (15.9%) in our study no tests were used. In these cases the diagnosis of *H. pylori* infection was based on symptoms and medical history.

In the group of patients with a pre-treatment specific diagnostic test (442/527), we looked at determinants associated with specific post treatment testing (154/442). We found that previous PPI use, a 60 mg daily lansoprazole dose and use of a quadruple schedule were determinants associated with post-treatment testing. These characteristics might reflect a group of patients previously not responding satisfactorily to PPIs and as a result justify post-treatment testing. Post-treatment testing was frequent (34.8%) in our study compared to 15% of the patients that were tested in the Scottish GP study [26]. Due to the fact that eradication rates are generally high, the necessity for confirmation is of minor importance, although routine verification of eradication seems less expensive than waiting for the disappearance of symptoms [17].

In our study, as many as 22 different regimens were reported, most of which were triple schemes (64.7%), followed by quadruple schedules (23.3%) and dual therapies (12.0%). Dual schedules were mainly used in 1994, prescription of triple regimens increased during the total study period from 20% to 80%, while quadruple schedules showed a slow increase in use from 20% to 20-30%. For specialists this pattern occurred about six months earlier compared to GPs. This pattern of a slower adoption by GPs compared to specialists has been described before and maybe related to less available information about new therapies and more conservative practice styles in general practice [22]. The Danish National Surveillance of *H. pylori* eradication therapy revealed less than 1% prescribed quadruple regimens from January 1994 to June 1996, which may be associated with the fairly late introduction of *H. pylori* eradication therapy [23].

The Maastricht Consensus Report recommends simple, well-tolerated therapies with eradication rates of over 80%. This group prefers a triple therapy for seven days, using a PPI and two of the following: clarithromycin, a nitro-imidazole (metronidazole or tinidazole) and amoxicillin [20]. The Dutch guidelines do not recommend a specific drug regimen; the choice of drug regimen depends on the local guidelines applicable [19]. Therefore, our findings illustrate that triple therapies being the most popular prescribed schedule, were in accordance with the European and Dutch recommendations in 52.0% and 64.7% of cases respectively. The duration of therapy for quadruple and triple regimens were in accordance with the recommendations, while for dual schedules a shorter duration of therapy was reported in 46.0% of cases. If different dosage schedules were taken into account, our 527 patients used a total of 67 different schedules. In 1995 the management of *H. pylori* infection was studied in 154 patients in 5 GP-practices in the United Kingdom. It emerged that 56 different schedules were used, the most frequently used schedule was a combination of omeprazole and amoxicillin [6]. Other studies indicate that there is still confusion about the indications for treatment and the treatment regimens that are likely to be effective in routine clinical practice [27].

When only patients with confirmed diagnoses and assessments of eradication with specific tests were taken into account, as is done in clinical trials, the overall eradication rate in our observational study was 86.6%, 69.2% in dual therapies, 84.4% in triple and 95.7% in quadruple schedules. These results are consistent with the findings of clinical trials [5, 6].

In conclusion, we explored 527 *H. pylori* eradication therapies in naturally occurring lansoprazole users. Regarding the indications for use, the physicians practised in about 70-75% according to the guidelines. Triple schedules, as recommended, were used in two out of three patients. During the study a change from prescribed dual to (specific) triple schedules was observed. These patterns were similar for patients evaluated by GPs and specialists. Pre-treatment diagnostic tests were often performed; the frequency and pattern of testing did not change over time. In general, eradication rates were high and comparable with results from clinical trials. However, post-treatment testing was frequent.

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Chapter 4.2

Continued use of the proton pump inhibitor lansoprazole following *Helicobacter pylori* eradication

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SUMMARY

Background: Therapies combining antibiotics and proton pump inhibitors (PPIs) have shown to be effective in clinical trials to eradicate *Helicobacter pylori* (*H. pylori)* in peptic ulcer patients. Because this evidence is mainly based on results of clinical trials in peptic ulcer patients, we assessed the incidence of continued use of a PPI after *H. pylori* eradication and evaluated determinants associated with continued use after *H. pylori* eradication therapies in daily clinical practice.
Methods: As part of a prospective observational follow-up study of 5,669 lansoprazole users, 258 patients treated with lansoprazole as part of *H. pylori* eradication therapy in daily clinical practice, were followed and evaluated. A case-control design was used to compare patients with continued use of lansoprazole versus patients with no continued use of lansoprazole after *H. pylori* eradication therapy. Continued use was defined as a new lansoprazole prescription more than 14 days after start of the *H. pylori* eradication therapy.
Results: Triple therapy was most commonly prescribed (57.4%), followed by quadruple (21.7%) and dual (20.9%) therapy. We found that 41.1% (106/258) of patients continued PPI treatment after *H. pylori* eradication therapy. Even one out of three peptic ulcer patients without GERD and treated with triple or quadruple therapies had continued PPI use.
Conclusion: Continued use may partly be expected by GERD in the diagnosis or use of sub-effective eradication therapies, but even one out of three peptic ulcer patients without GERD and treated with triple or quadruple therapies had continued PPI use. Additional research is necessary to investigate the impact of compliance and possibly other determinants on continued PPI use.

INTRODUCTION

Therapies combining antibiotics and PPIs have shown to be effective in clinical trials to eradicate *H. pylori* in peptic ulcer patients. Triple and quadruple therapies provide the highest eradication rates of > 90%, while for dual therapies overall eradication rates with a maximum of 60-80% are commonly accepted [1-5]. Because this evidence is mainly based on results of clinical trials in peptic ulcer patients, we assessed the incidence of continued use of a PPI after *H. pylori* eradication and evaluated determinants associated with continued use after *H. pylori* eradication therapies in daily clinical practice. In such a setting there will be among others a variety of prescribed treatment therapies influencing outcomes considerably [6].

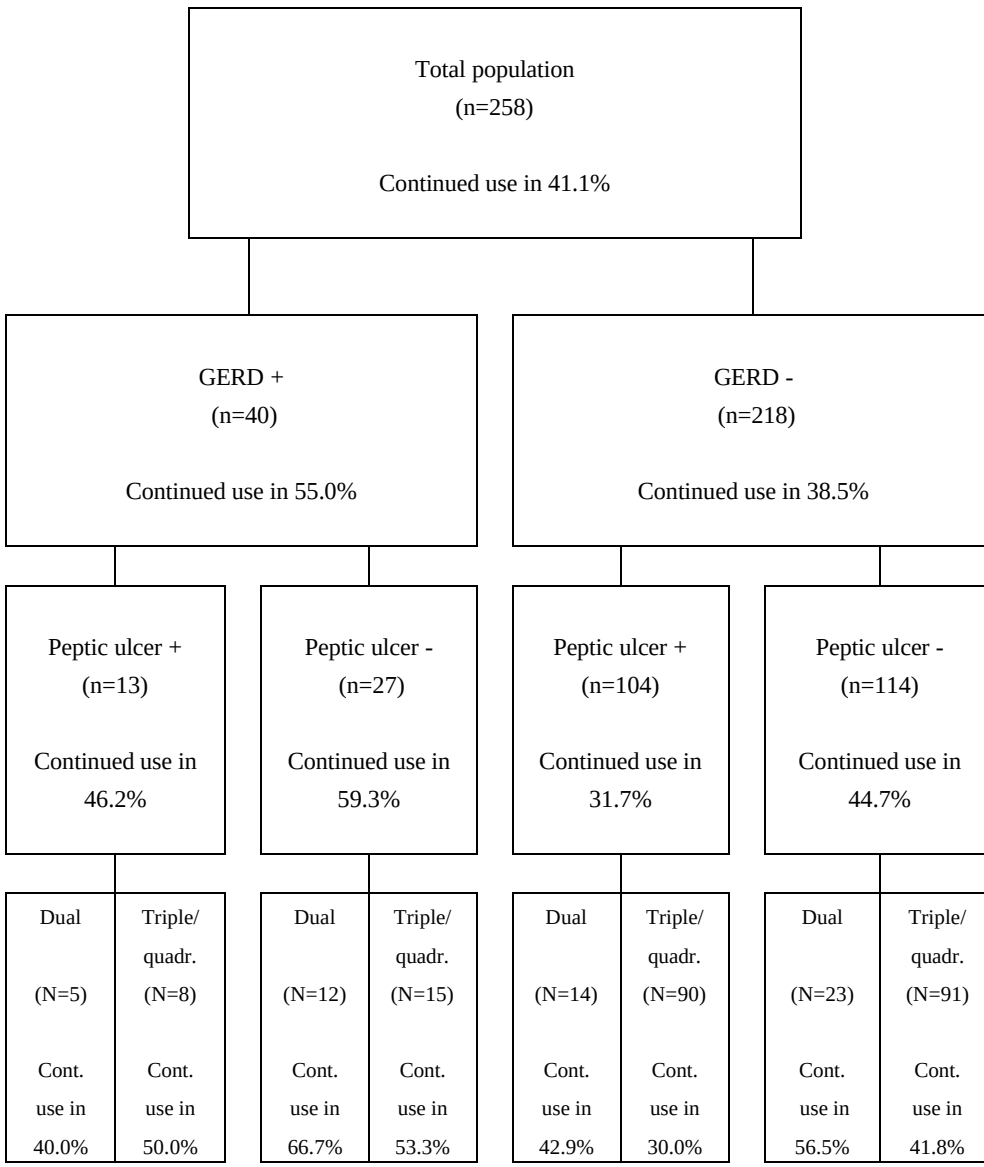
MATERIALS AND METHODS

As part of a prospective observational follow-up study of 5,669 lansoprazole users, 258 patients treated with lansoprazole as part of *H. pylori* eradication therapy in daily clinical practice, were followed and evaluated [7]. Physicians collected data including, age, gender, primary indication of lansoprazole prescription, past use of acid related drugs, eradication regimen and eradication success or failure. No specific tests were requested from the physician with regard to the primary diagnosis and the method used to assess eradication. A case-control design was used to compare patients with continued use of lansoprazole versus patients with no continued use of lansoprazole after *H. pylori* eradication therapy. Continued use was defined as a new lansoprazole prescription more than 14 days after start of the *H. pylori* eradication therapy. Baseline comparisons were calculated yielding odds ratios with a confidence interval of 95%. Odds ratios were adjusted for all other given determinants using conditional logistic regression.

RESULTS AND DISCUSSION

Triple therapy was most commonly prescribed (57.4%), followed by quadruple (21.7%) and dual (20.9%) therapy. These results were in accordance with literature stating triple therapy as standard therapy [2]. In total, 20 different combinations of drugs were used, increasing to over 50 individual therapy regimes when dosages were taken into account. In the majority of patients the duration of eradication therapy was 5 to 7 days or, less frequently, 8 to 14 days.

Figure 1
Continued use of PPIs after *H. pylori* eradication therapy by primary diagnosis and eradication schedule in 258 patients



We found that 41.1% (106/258) of patients continued PPI treatment after *H. pylori* eradication therapy (Figure 1). Patients with only GERD and patients treated with dual eradication therapies continued their PPI therapy most frequently in respectively 55.0% and 53.7%. Patients with a peptic ulcer without GERD and treated with quadruple and triple eradication therapies (n=90) showed continued use in 30.0%. A proportion of these patients with duodenal ulcer and treated for *H. pylori* may have developed GERD after cure and therefore a PPI was prescribed [8]. A small number of patients with gastric ulcer and treated for *H. pylori* may not have achieved cure yet, as in these patients a short-term treatment up to 8 weeks is recommended [9]. In general, PPIs may be prescribed as preventive therapy in peptic ulcer patients requiring chronic NSAID treatment [10]. However, we found only 5.1% (2/39) of patients using long-term NSAIDs among the patients with peptic ulcers and continued use.

As shown in Table 1, GERD without peptic ulcer as diagnosis was significantly associated with continued use with an adjusted odds ratio (95% CI) of 2.8 (1.1-7.2). In patients with only GERD, continued PPI use is expected after *H. pylori* eradication therapy as maintenance therapy to prevent recurrences [11]. Of patients with 'other' diagnoses, 44.7% (51/114) continued PPI treatment. A lack of symptom relief has been reported in patients with nonulcer dyspepsia [12]. However, contrasting results exist, as also a symptomatic benefit from eradicating *H. pylori* in patients with nonulcer dyspepsia has been described [13]. Dual therapy was more frequently but not significantly reported in patients with continued PPI use (27.4%) versus patients with no further PPI use (16.5%). Patients treated with dual *H. pylori* eradication therapies may continue their PPI therapy due to lower eradication rates of dual therapies compared to triple and quadruple therapies [1-5]. In patients with continued PPI use, past use of H_2-receptor antagonists was less common (adjusted odds ratio (95% CI): 0.6 (0.3-1.0); an association with the primary diagnosis ulcer could not be established.

Evaluation by general practitioner or specialist, as well as gender and age did not significantly differ between patients continuing PPI use and patients with no further PPI use. Eradication was achieved in 80.3% (53/66) of the continued users versus 91.1% (82/90) of the patients with no further lansoprazole use; this difference was not significant. In the remaining patients eradication success or failure was not assessed. So, in a daily clinical practice setting, many patients with *H. pylori* eradication continued lansoprazole treatment (41.1%).

Table 1
Determinants of continued use of PPIs after *H. pylori* eradication therapy

	Continued use N=106 (%)	No further use N=152 (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Female	45 (42.5)	67 (44.1)	0.9 (0.6-1.5)	0.8 (0.5-1.4)
Age				
0-45	36 (34.0)	48 (31.6)	(reference)	(reference)
45-60	36 (34.0)	56 (36.8)	0.9 (0.5-1.6)	0.8 (0.4-1.5)
> 60	34 (32.1)	48 (31.6)	0.9 (0.5-1.7)	0.9 (0.5-1.8)
Specialist	79 (74.5)	116 (76.3)	0.9 (0.5-1.6)	1.1 (0.5-2.1)
Past use				
None of both	46 (43.4)	51 (33.6)	(reference)	(reference)
H_2-receptor antagonist	50 (47.2)	92 (60.5)	0.6 (0.4-1.0)	0.6 (0.3-1.0)
PPI	16 (15.1)	24 (15.8)	0.9 (0.5-1.9)	0.9 (0.4-1.8)
Primary diagnosis				
Ulcer without GERD	33 (31.1)	71 (46.7)	(reference)	(reference)
Ulcer with GERD	6 (5.7)	7 (4.6)	1.8 (0.6-5.9)	1.6 (0.5-5.4)
GERD without peptic ulcer	16 (15.1)	11 (7.2)	3.1 (1.3-7.5)	2.8 (1.1-7.2)
Other **	51 (48.1)	63 (41.5)	1.7 (1.0-3.0)	1.7 (0.9-3.1)
Eradication regimen				
Quadruple	18 (17.0)	38 (25.0)	(reference)	(reference)
Triple	59 (55.7)	89 (58.6)	1.4 (0.7-2.7)	1.2 (0.6-2.5)
Dual	29 (27.4)	25 (16.5)	2.4 (1.1-5.3)	1.9 (0.8-4.5)

* Other primary diagnosis e.g. ‘gastritis’, 'duodenitis'
** Adjusted for all other determinants

This may partly be expected by GERD in the diagnosis or use of sub-effective eradication therapies, but even one out of three peptic ulcer patients without GERD and treated with triple or quadruple therapies had continued PPI use. There are no indications that other PPIs demonstrate different user profiles [14]. Additional research is necessary to investigate the impact of compliance and possibly other determinants on continued PPI use [15].

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Chapter 5

Safety of proton pump inhibitor treatment

Chapter 5.1

Safety review of 10,008 users of lansoprazole in daily practice

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SUMMARY

Background: Soon after the introduction of the proton pump inhibitor (PPI) lansoprazole a 4-year observational follow-up study was started to evaluate the safety of this drug in naturally occurring groups of patients in the Netherlands. Results of this study were compared with clinical trial data and the limited published data from observational studies.
Methods: A prospective, observational study in which patients with a new episode of lansoprazole use were followed during use with a maximum of two years. All (adverse) events during use were documented by the prescriber, irrespective of possible association with lansoprazole therapy.
Results: 805 General practitioners (GPs) and 266 specialists included a total of 10,008 lansoprazole users with a broad range of diagnoses. Of all patients, 17.4% reported one or more adverse events. The profile and frequency of reported adverse events was consistent with results from clinical trials and other observational studies. The most frequently reported adverse events were diarrhoea, headache, nausea, skin disorders, dizziness and generalised abdominal pain/cramps. There was no new evidence of rare adverse events. Furthermore, no lansoprazole related unlabeled adverse events of clinical significance were recorded.
Conclusions: Although the patterns of use of lansoprazole in daily practice deviated to some extent from the diagnoses in the information leaflet, lansoprazole was found to have a highly acceptable safety profile in this large naturally occurring group of users. Reporting rates were higher soon after introduction before falling to a lower stable level.

INTRODUCTION

Lansoprazole is a PPI introduced on the Dutch market at the end of 1993 indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers [1]. Lansoprazole was firstly introduced as a 30 mg capsule, while in January 1996 a 15 mg capsule was launched for the same diagnoses. At the time of introduction, lansoprazole had been evaluated in several thousands of patients enrolled in clinical trials [2]. The most commonly reported adverse events in clinical trials included headache, diarrhoea, nausea, dizziness, vomiting, constipation, asthenia and flatulence [3, 4]. Rarely reported adverse events associated with PPIs in general were dry mouth, gynaecomastia, acute liver injury, visual disorders and acute polyarthralgia, although regarding the latter two events the relationship with the use of lansoprazole is still under discussion [5-11]. Besides data from clinical trials, estimates of the 'real-world' safety profile were and still are scarce [12, 13]. Spontaneous case reports stem from undefined, exposed populations, in which data was collected in a non-standardised manner. Epidemiological studies provide more reliable measures of risk and can place spontaneous reports in perspective [14]. This was one of the reasons to set up a large epidemiological prospective follow-up study of lansoprazole users in daily clinical practice in The Netherlands with the aim to assess the safety, efficacy and pattern of use of lansoprazole. The study started directly after introduction of the drug on the market. General results of the first two years of this study are described elsewhere [15]. In this article we focus on the reporting of adverse events during lansoprazole use by a large group of patients found in daily clinical practice, including patients of any age with various diagnoses and underlying diseases. As described by Weber, higher spontaneous reporting rates exist soon after marketing of a drug and this pattern persists for about two years before falling to a stable lower level [16]. This has even been reported despite the usual trend of increasing prescribing rate [17]. A second objective therefore was to investigate whether reporting rates of adverse events change in time.

MATERIALS AND METHODS

Design

A prospective, observational follow-up study was carried out in 10,008 lansoprazole users in the Netherlands during the first four years after marketing from

January 1994 until April 1998 [15]. No inclusion or exclusion criteria were applied other than the use of lansoprazole prior to entry into the study. The study design included a population as representative as possible of the general population (in daily practice lansoprazole was prescribed by specialists as well as GPs), a non-interventional design, a clear separation in time between the prescribing of lansoprazole and the inclusion of the patient in the study in order to minimise the influence of the study on the prescribing behaviour and the evaluation, following SAMM guidelines [18]. The protocol was approved by the Independent Ethical Committee of the Utrecht University Medical Centre. The overall design has been described in detail elsewhere [15].

Patients

All patients having used or using lansoprazole were included in the study at the first or any later follow-up visit after lansoprazole was prescribed. Patients agreed to participate by giving their free informed consent allowing access to all relevant clinical and medication data and storage and analyses of these data. No further selection criteria were considered, meaning that every lansoprazole user independent of diagnosis (labelled or unlabeled, diagnostically tested or not) could enter the study.

Measurements

The physician collected data at the inclusion visit and at each follow-up visit during lansoprazole therapy with a maximum follow-up of two years using standardised questionnaires. The data collection was designed not to influence normal procedures by following routine visits and no preset visit schedule. General characteristics such as age, gender, specialism of evaluating physician, diagnosis of lansoprazole therapy, start date of lansoprazole use and evaluation date were recorded. An adverse event was defined as any undesirable experience including intercurrent events, drug reactions and clinical abnormalities or clinically significant laboratory test abnormalities, occurring during the study. During follow-up, all (adverse) events irrespective of association with lansoprazole therapy were documented, including a description of the event, the date of onset and if available the date the event stopped. Furthermore, the severity of the adverse events was reported as perceived by the physician and classified as mild, moderate, severe or unknown. According to the ICH/GCP guidelines, a serious adverse event

was defined as an event resulting in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is congenital anomaly/birth defect [19]. The association of the adverse event with the use of lansoprazole as assessed by the physician was documented as unlikely, possible, probable or unknown. Furthermore, it was stated whether any action was taken due to the adverse event and labelled as no action, lansoprazole dose reduction or discontinuation, other therapy, other action or unknown. Where the same event occurred more than once in one patient, only the first episode was used in the calculations. Labelled adverse events included events described in the product information and unlabeled events otherwise.

Analysis

Results were tabulated in absolute values and percentages. Incidence densities were calculated during follow-up as the number of reported adverse events per 1,000 patient months of exposure. The exposure period was defined as the period from start of therapy until end of lansoprazole therapy or end of follow-up when still on therapy. All statistical analyses were performed using SAS statistical package.

RESULTS

Patient enrolment started in January 1994 following the introduction of lansoprazole in the Netherlands in September 1993 and ended April 1998. In total 266 specialists and 805 GPs included respectively 3,846 and 6,162 patients. In Table 1 general characteristics of the 10,008 included patients are shown, including gender and age distributions. The majority of patients had gastro-oesophageal reflux disease as diagnosis for lansoprazole therapy (53.6%) or any ulcer (14.5%), whereas in 29.8% other diagnoses were reported such as ‘gastritis’, ‘dyspepsia’ and ‘duodenitis’. Most patients were treated with 30 mg lansoprazole per day (88.6%), while 5.7% had a prescription of ≤ 15 mg and 5.6% of ≥ 60 mg per day. Of all lansoprazole users 82.6% reported no adverse events during lansoprazole exposure (n=8,267). A total of 11.9% reported one adverse event, 3.8% reported two adverse events. During the exposure period, 1.7% reported three or more adverse events with a mean of 3.4 events per patient. Of patients using ≤ 15 mg, 30 mg and ≥ 60 mg lansoprazole per day respectively 12.0%, 17.5% and

20.8% reported adverse events. Furthermore, 4 of the 9 patients with an unknown dosage regimen reported adverse events. There was a significant association between daily dose and the reporting of adverse events ($p<0.001$).

Table 1
General characteristics of 10,008 lansoprazole users

	N=10,008	%
Men	4,864	48.6
Women	5,144	51.4
Age (years)		
0-30	660	6.6
30-45	2,196	21.9
45-60	3,279	32.8
60-75	2,768	27.7
> 75	1,106	11.1
Diagnosis of lansoprazole therapy		
GERD without ulcer	5,366	53.6
Other*	2,982	29.8
Ulcer without GERD disease	1,454	14.5
Ulcer with GERD	201	2.0
Unknown	5	0.1
Daily lansoprazole dose		
≤ 15 mg	566	5.7
30 mg	8,870	88.6
≥ 60 mg	563	5.6
Unknown	9	0.0
Patients reporting adverse events		
No adverse events	8,267	82.6
1 adverse event	1,186	11.9
2 adverse events	381	3.8
> 2 adverse events	174	1.7

* Other diagnosis of lansoprazole therapy e.g. ‘gastritis’, ‘duodenitis’

As is shown in Table 2, in total 2,539 adverse events were reported. Of all adverse events, 49.4% was possibly and 26.6% probably related to the lansoprazole exposure, as assessed by the physician. In a majority of the events (57.8%) no action was taken, in 5.6% the lansoprazole dosage was reduced and in 29.0% lansoprazole therapy was discontinued.

Table 2
Characteristics of adverse events

	N=2,539	%
Evaluating physician		
GP	1,364	53.7
Specialist	1,175	46.3
Severity of adverse events		
Mild	1,181	46.5
Moderate	983	38.7
Severe	366	14.4
Unknown	9	0.4
Association of adverse event with lansoprazole		
Unlikely	600	23.6
Possible	1,255	49.4
Probable	675	26.6
Unknown	9	0.4
Action taken		
None	1,467	57.8
Stop of therapy	737	29.0
Switch of therapy	171	6.7
Dose reduction	141	5.6
Other action	4	0.2
Unknown	19	0.7

Table 2
(continued) Characteristics of adverse events

	N=2,539	%
Specification per body system		
Digestive system	1,323	52.1
Nervous system	441	17.4
Skin and appendices	230	9.1
Body as a whole	114	4.5
Musculo-skeletal system	94	3.7
Psyche	72	2.8
Endocrine/metabolic/nutritional	71	2.8
Other system	194	7.6

According to the physician nearly all adverse events were of either mild (46.5%) or moderate (38.7%) severity, whereas 14.4% were characterised as severe adverse events. Most of all 2,539 adverse events concerned the digestive system (52.1%), nervous system (17.4%) and skin and appendices (9.1%). In 41 patients (0.4%) a serious adverse event as defined by the ICH/GCP guidelines was reported, including malignant neoplasm (n=13), cardiovascular disease (n=8), rash (n=2), and pneumonia (n=2) [19]. Of all serious adverse events, 60% included hospitalisations. Regarding all serious events, no definite causal relationship with lansoprazole was assessed after evaluation.

Distributions of the most frequently (≥ 0.25% or in other words ≥ 25 events) observed adverse events are listed in Table 3 in percentages of all patients. The most frequently reported adverse events were diarrhoea (3.7%), headache (2.5%) and nausea (2.2%). When compared to available clinical data (expected frequencies), the frequencies of diarrhoea, nausea, constipation and dizziness were similar [3, 4]. The majority of the skin disorders (1.5%) included pruritus and/or rash. In our study, headache and vomiting were reported less frequently than expected from data of clinical trials. In patients aged 65 years or over, we found 2.1% of patients reporting headache versus 1.6% and 4.0% in clinical trials [3, 4].

Table 3
Frequencies of adverse events (N≥25) observed in 10,008 lansoprazole users and compared with clinical trial data

Specification adverse event	Observed N	Observed %	Expected* %	Expected** %
Diarrhoea	368	3.7	3.2	3.5
Headache	246	2.5	4.7	8.8
Nausea	222	2.2	1.4	2.0
Vomiting	31	0.3		1.4
Dizziness	183	1.8	1.0	1.6
Generalized abdominal pain/cramps	171	1.7	2.2	
Flatulence/gas pain/belching	128	1.3		
Skin disorders	203	2.0	1.7	
Constipation	103	1.0	1.1	1.0
General weakness/tiredness	50	0.5	<1	
Symptoms/complaints mouth/tongue/lip	99	1.0		
Change in feces/bowel movements	77	0.8		
Disturbances of sleep/insomnia	30	0.3	<1	

* Colin-Jones DG. Safety of lansoprazole. Aliment Pharmacol Ther 1993;7 Suppl:56-60.

** Colin-Jones DG. Safety of lansoprazole. Br J Clin Pract 1994;Suppl 75:58-66.

To give estimates of ‘real-world’ frequencies of reported adverse events we calculated incidence densities (IDs). In Table 4, IDs of the top 10 of reported events were compared with expected IDs as described in the PEM study [13]. In our study, 10,008 patients were evaluated during a mean duration of therapy of 3.42 months, in the PEM study 17,329 patients were followed during a mean duration of lansoprazole use of 3.34 months. Our top 10 included 7 adverse events of the top 10 of the PEM study. In addition, we found very similar IDs compared to these PEM data. Only headache and dizziness was slightly more frequently reported in our study compared to the PEM results.

Table 4
Incidence Densities (ID) of the top 10 of adverse events per 1,000 patient months of use during the total treatment period as observed in 10,008 lansoprazole users and compared with observational data of 17,329 lansoprazole users *

Specification adverse event	Observed N	Observed ID per 1,000	Expected ID per 1,000
Diarrhoea	368	10.7	9.9
Headache	246	7.2	4.6
Nausea/vomiting	233	6.8	5.9
Dizziness	183	5.3	2.6
Generalized abdominal pain/cramps	171	5.0	5.7
Flatulence/gas pain/belching	128	3.7	No info
Pruritus	127	3.7	1.4
Constipation	103	3.0	1.8
General weakness/tiredness	50	1.5	3.0
Joint pain	16	0.5	3.3

* Freemantle SN, Pearce GL, Wilton LV, Mackay FJ, Mann RD. The incidence of the most commonly reported events with 40 newly marketed drugs - a study by Prescription-Event Monitoring. Pharmacoepidemiol Drug Safety 1997;6;Suppl 1:1-52.

Regarding rarely reported adverse events known from case reports and clinical trials with PPIs we found gynaecomastia in 2 patients (both assessed mild in severity, one not drug related and one possibly drug related). One case of liver disorder, mildly severe and not assessed as lansoprazole related and one moderate severe and possible lansoprazole related liver function abnormality was documented. Acute liver injury and haemolytic anaemia were not reported during this study. A total of 42 patients reported dry mouth. The severity was most frequently mild (n=24), followed by moderate (n=15) and severe (n=3); most often a possible relationship with use of lansoprazole (n=30) was reported, in 8 patients a probable relationship and in the 4 others an unlikely relationship with use of the drug. We found 19 patients with acute polyarthralgia, of which 15 were probably or possibly lansoprazole related, 4 severe and 8 requiring a lansoprazole dose reduction or discontinuation.

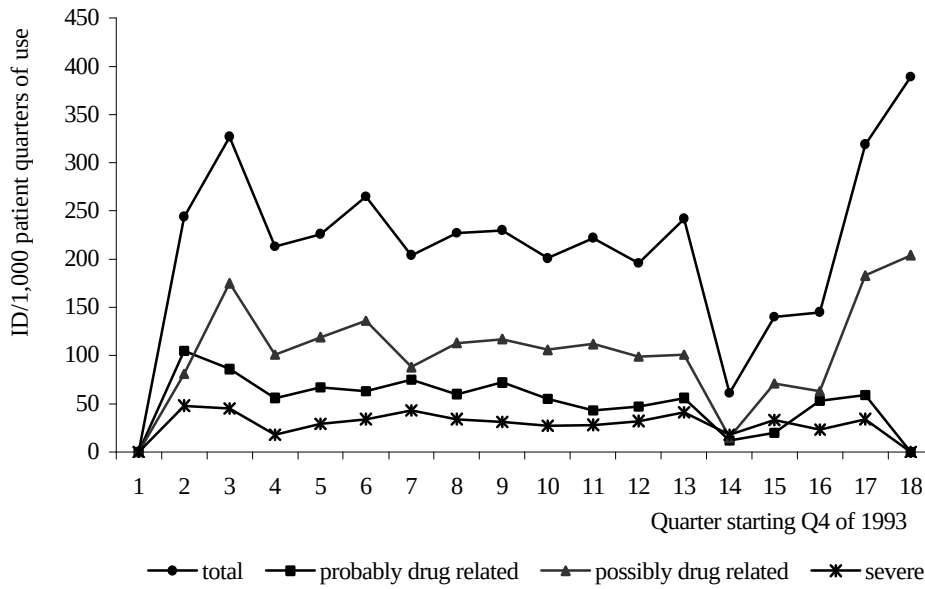
Ocular events were reported in 25 patients, including abnormal eye sensations (n=12), visual symptoms/complaints (n=11), conjunctivitis (n=1) and symptoms/complaints eyelids (n=1). The reported abnormal eye sensations included itching, dryness, swelling, redness and burning/tingling. The visual symptoms/complaints included blurred vision (n=7), temporary blindness/severe vision disorder (n=2), spotting during car driving (n=1) and acute blindness in one patient with a medical history of temporal arthritis and polymyalgia rheumatica (n=1). Of all vision disorders, three events were deemed probably related (i.e. itching, conjunctivitis, other symptoms/complaints eyelids) and 13 events possibly related with the use of lansoprazole (i.e. once blurred vision and 12 patients with abnormal eye sensations), whereas 9 events were unlikely related with use of the drug. The incidence density of lansoprazole related vision disorders was 10.5 per 10,000 person years (i.e. 2.9 per million treatment days).

There were 1,930 probably or possibly lansoprazole related events of all 2,539 adverse events. 509 of these 1,930 events were not labelled in the applicable product information for lansoprazole (26.4%). Most unlabelled events were reported in a frequency of less than 25 (i.e. less than 2.5 per 1000). However, flatulence/gas and pain/belching was reported 108 times, change in faeces/bowel movements 66 times and symptoms of the mouth such as sensitive tongue and changes in taste 35 times. 69 of the 509 unlabeled events were assessed as severe adverse events. Nearly all of these 69 events were reported only once or twice and of clinical insignificance. There were three clinically significant events of the 69, namely malignant neoplasm oesophagus (n=3), death (n=2) and malignant neoplasm prostate (n=1). These six events were reported by the physicians as serious adverse events [19]. The conclusion after review by experts was that no or no definitive causal relationship between these serious adverse events and the treatment with lansoprazole was established. Furthermore, flatulence/gas pain/belching was reported seven times and baldness/losing hair three times as probably or possibly lansoprazole related, severe and unlabeled events.

To analyse the influence of time after registration on the reporting of adverse events IDs were calculated for subsequent periods of time. During the first 2 years 5,669 patients were followed during 21,084 months of lansoprazole use, whereas in the second period 4,339 patients were evaluated during 13,224 months of use. The ID per 1,000 patient months of use of any adverse event was 74.0 during the total study period. The ID during the first 2 years after launch

(1994-1995) was 78.7 and the ID of the next two years was 66.4. Especially probably drug related events were less frequently reported in the last 2 years of the study (ID 14.8) compared to the first 2 years (ID 22.7).

Figure 1
Incidence Densities of reporting of adverse events (n=2,539) for subsequent quarters



To analyse this influence of time in more detail, IDs were calculated for subsequent quarters (periods of three months) starting quarter 4 of 1993. As can be seen in Figure 1, the IDs were high soon after launch (quarter 2 and 3) and became stable in the following period. This pattern was even more marked for severe and/or probably lansoprazole related adverse events. Results of the latest quarters (Q14 up to Q18) showing a rapid decrease followed by a quick increase of IDs were reasonably artefacts due to a low number of exposure months and a delayed cessation of the study.

DISCUSSION

The main objective of this study was to assess the safety of lansoprazole in a population composed by users in daily clinical practice and to evaluate the influence of time after registration on the reporting of adverse events.

In clinical trials patients receiving the usual daily dose of 30 mg of lansoprazole reported one or more adverse events in 30.0% [2]. In this observational study 17.4% of the 10,008 evaluated patients reported one or more adverse events. There was a significant positive association between lansoprazole dose and the reporting of adverse events. It was expected that in this observational study reporting rates were lower compared to clinical trials due to the study design, available information on labelled events etc.

In general, the adverse events during lansoprazole use were mild and self-limiting. It was seen that in 30% of all adverse events the dose of lansoprazole was stopped and in 6% the dose was reduced. In nearly 50% a possible and in one out of four a probable relationship with the use of lansoprazole was documented by physician. The reporting rate of serious adverse events of 0.4% was comparable with the 0.6% as reported in clinical trials [4]. No serious adverse events related to lansoprazole were observed in the study group.

The overall safety profile of lansoprazole in this study was similar to the profile of events in clinical trials and observational studies with lansoprazole and comparative agents [2-4, 12, 13, 20]. Frequencies were comparable with results from clinical trials with the major exception that we found lower rates of headache and vomiting. In clinical trials headache was reported in 4.7% and 8.8% respectively of all patients and in 1.6% and 4.0% in patients aged 65 years or over using pooled data from international trials [3, 4]. The proportion of patients aged 65 years or over was considerably (three times) higher in our study compared to clinical trials, which may be an explanation of our lower rate of reporting headache.

In general we found very similar IDs as found in the PEM study, although comparisons between results of observational cohort studies are difficult due to multiple possible differences. Possible existing differences include e.g. diagnoses for which the drug has been used, prescriber, prescribed doses, duration of use, age

and sex distributions, publicity, calendar year, initial rate of sale, different pattern of usage of a drug [12, 13, 21].

Regarding rare adverse events we found similar profiles as described in literature [5-11]. From clinical trials, very few numbers are available about e.g. dry mouth, gynaecomastia to make comparisons in reporting rates. In 3 patients blindness/severe vision disorder was documented. None of these events were related to lansoprazole use, as assessed by the physician, while according to the WHO database, the ID of drug related blindness/severe vision events was 0.022 per million treatment days [8]. Garcia Rodriguez did investigate ocular events in more detail through a retrospective cohort study in general practice with omeprazole [9]. He found no inflammatory lesions, whereas vascular lesions of the eye (e.g. amaurosis fugax) were found with an ID of 2.8 per 10,000 person years. In our study the ID of any drug related vision disorder was 10.5 per 10,000 person years. However, none of these disorders were classified as severe, as assessed by the physician. Besides, patients with certain medical histories e.g. eye disorders, cancer, hypertension, diabetes were excluded from the cohort by Rodriquez and not by us.

In general practice, it is known that unlabelled drug related adverse events are more frequently reported compared to labelled events [22]. There is a selective reporting bias for adverse events with greatest clinical concern. In our study, we found three probably or possibly lansoprazole related and unlabeled events reported over 25 times, namely flatulence/gas pain/belching (n=108), change in faeces/bowel movements (n=66) and symptoms tongue (n=35). Many of these events could result from the treatment as well as from the disease.

Regarding the time trend, we found higher reporting rates soon after marketing of the drug before falling to a lower stable level. Especially probably lansoprazole related adverse events were more frequently reported during the first year after introduction. It is consistent with Weber's theory that the reporting of adverse events to a new drug does not proceed at a uniform rate, but higher spontaneous reporting rates exist soon after marketing of a drug and this pattern persists before falling to a stable lower level [17].

In conclusion, this 4-year observational follow-up study was started to evaluate the safety of lansoprazole in naturally occurring groups of patients in the Neth-

erlands. 805 GPs and 266 specialists included a total of 10,008 lansoprazole users with a broad range of (un)registered diagnoses. Of all patients, 17.4% reported one or more adverse events. The profile and frequency of reported adverse events was consistent with results from clinical trials and observational studies, whereas the proportion of patients aged 65 years or over was considerably (three times) higher in our study compared to clinical trials. The most frequently reported adverse events were respectively diarrhoea, headache, nausea, skin disorders, dizziness and generalised abdominal pain/cramps. In our study, headache and vomiting were reported less frequently than expected from data of clinical trials. There was no new evidence of rarely reported adverse events. Furthermore, no lansoprazole related unlabeled adverse events of clinical significance were recorded.

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Chapter 5.2

Incidence of headache in lansoprazole users: which determinants contribute?

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SUMMARY

Background: In clinical trials, headache is one of the most frequently reported adverse events (frequency 1.3-8.8%), while results of one observational study indicate that headache is the fifth most frequently reported adverse event (incidence densities 2.5-4.6 per 1,000 patient months of exposure) during proton pump inhibitor (PPI) use. However, there are no observational studies performed regarding the occurrence and features of headache during use of PPIs in daily practice. For this reason this study was set up with the aim to assess the incidence and characteristics of headache and to investigate possible associated co-factors in PPI users in daily practice.

Methods: Data were used from a prospective, observational study in which 10,008 lansoprazole users were followed over time. The study was designed according to the SAMM guidelines. A nested case-control design was used to compare PPI users reporting headache with PPI users reporting no headache.

Results: The frequency of headache was 2.5% and the incidence density 7.2 per 1,000 patient months of PPI use. Tension headache was seen in two out of three patients with headaches and migraine in the remaining patients. The analysis of co-factors revealed that women, patients with previous use of analgesics and patients reporting several adverse events, were at risk to develop headache during PPI use. Patients with headache also, significantly more often, reported diarrhoea, nausea and dizziness. A de-challenge of PPI therapy resulted in a cessation or reduction of the headache in 80.0% (20/25).

Conclusion: In conclusion, as can be expected headache was reported less frequently in this study compared to clinical trials with lansoprazole. The incidence density was comparable with other observational data of lansoprazole and omeprazole users. The most commonly reported type of headache during lansoprazole use was tension headache. Besides several commonly accepted co-factors such as female gender and a history of analgesic use, we also found the reporting of other adverse events to be associated with the reporting of headache during lansoprazole use. The cessation of headache after a discontinuation of use of the PPI and the observed dose relationship suggested that headache was indeed a side-effect of lansoprazole use.

INTRODUCTION

The PPI lansoprazole was introduced in The Netherlands in the fall of 1993 and is indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers. The tolerability of PPIs has been thoroughly investigated in (randomised) clinical trials and headache is the most common adverse event reported, in 2.9-6.9% of omeprazole users, 3.8-8.8% of lansoprazole users, 1.3% of pantoprazole users and 2.4-6.0% of rabeprazole users. [1-6]. Estimates of the 'real-world' frequency and characteristics of headache as an adverse event during lansoprazole use are scarce. Such epidemiological studies with large groups of complex patients followed in daily practice provide more reliable measures of risk compared to clinical trials [7]. In the PEM study, the Incidence Density of headache during lansoprazole and omeprazole use was the fifth most often reported adverse event, in 4.6 and 2.5 per 1,000 patient months of exposure respectively [8]. The mechanism of headache in lansoprazole users, if any is yet unclear [1, 2]. Also, headache is shown to be a risk factor for self-reported peptic ulcers [9]. Co-factors associated with the occurrence of headache in the general population may be present such as younger age, female sex, caffeine consumption, co-morbidity (myocardial ischemia, stroke, hypertension and arthritis), previous episodes of headache, drug exposure and co-medication [10-12].

Furthermore, it must taken into account that results of an observational study on newly marketed drugs indicated that headache is reported in the top ten of adverse events of all 40 investigated drugs [8].

Therefore, this study was set up to investigate the incidence and characteristics of headache and to identify the value of co-factors associated with headache in naturally occurring lansoprazole users. Analysis of co-factors associated with the occurrence of headache may lead to identification of patients at risk.

MATERIALS AND METHODS

Design

The study data were derived from a prospective follow-up study conducted in the Netherlands in 10,008 naturally occurring users of lansoprazole during the first four years after introduction (January 1994 until April 1998). The study protocol

was designed according to the SAMM guidelines (guidelines for company-sponsored Safety Assessment of Marketed Medicines) on design of postmarketing safety studies and approved by the Medical Ethical Committee of the Utrecht University Medical Centre [13]. Methods of this study have been described in detail previously [14].

Data were analysed according to a nested matched case-control design with a 1:1 or 1:2 ratio for cases and controls. Retrospectively, cases were defined as lansoprazole users reporting headache as an adverse event. The preceding patient, of the same evaluating physician, not reporting headache during the total follow-up period was taken as the matched control, in order to limit observer bias [15]. In case the so-defined preceding control patient was not available, the next available patient of the same physician served as the control.

Patients

Patients were prescribed lansoprazole as part of daily practice. At any follow-up visit after the first prescription of lansoprazole, patients still using or having used lansoprazole were eligible for inclusion. Patients had to give their free written informed consent. No additional in- or exclusion criteria were considered [14].

Measurements

Data were collected at the inclusion visit and at follow-up visits thereafter during lansoprazole therapy by reviewing the medical file and by patient questionnaire. There was no further interference due to the study during the patient visit. The daily practice situation was followed as closely as possible. No additional diagnostic tests were requested from the physician with regard to the indication or any co-morbidity.

Baseline patient characteristics including age, gender, smoking habits and alcohol intake were recorded at the inclusion visit. Moreover information was obtained about the daily dose of lansoprazole, indication for use and relevant co-morbidity. All (adverse) events irrespective of being linked to lansoprazole therapy were documented including the onset, severity, possible relationship with lansoprazole use, action taken and outcome. The physician reported severity and association of the events.

In addition, for lansoprazole users reporting headache from January 1996 onwards (n=83), as well as for the preceding patient of the same physician supplementary questionnaires were completed. We received 35 completed questionnaires from patients with headaches (response 35/83, 44.6%). Two of the 35 questionnaires were not valid (5.7%), because the physician reported that during lansoprazole use no headache was reported in contradiction with information received at an earlier stage. At the same time, the same physicians were requested to complete an equal number of similar questionnaires for patients not reporting headache and evaluated from January 1996 onwards. We received 42 completed questionnaires (response 42/83, 50.6%). In six of the 42 questionnaires the physician reported that headache was reported during lansoprazole use after the study period. These patients were excluded. Our response rate was comparable with the overall response rate of 53% found in the UK after requesting postmarketing data on new drugs [16].

The patient questionnaires were used to collect specific data about characteristics of episodes of headache three months prior to and during lansoprazole intake, including duration, onset, location and a thorough symptom checklist. Furthermore, possibly related co-factors including prior and current use of alcohol, caffeine and analgesics were recorded. The symptom checklist was used to classify headache into migraine, cluster headache and/or tension headache, according to international guidelines [17].

Complete prescription medication histories were obtained through pharmacy records from six months retrospectively and during the lansoprazole therapy. The physician requested the appropriate pharmacy to collect the pharmacy records. Drugs used were coded according to the anatomical-therapeutic-chemical (ATC) classification [18].

Analysis

Current drug use was determined as drug use at the moment of onset of headache, whereas past drug use was defined as drug use during the six months prior to the onset of headache. For each control without headache the moment of onset of headache of the matched case was used as a reference value to estimate current and past use of co-medication and current doses.

Results were tabulated in absolute values and percentages. Baseline comparisons were calculated yielding crude and adjusted odds ratios with a confidence interval of 95%. Adjusted odds ratios were calculated using conditional logistic regression. Incidence densities were calculated during follow-up as the number of reported adverse events per 1,000 patient months of exposure. The exposure period was defined as the period from start of therapy until the end of lansoprazole therapy or the end of follow-up when still on therapy. Statistical significance was assumed at p-value < 0.05. All statistical analyses were performed using SAS and EGRET statistical packages.

RESULTS

This study was set up to investigate the incidence and characteristics of headache and to identify the value of co-factors associated with headache in 10,008 naturally occurring lansoprazole users. The frequency of headache in daily practice of lansoprazole users was 2.5% (246/10,008) and the incidence density 7.2 per 1,000 patient months of use.

The reporting of headache was dose related. Headache was reported in 2.7% (15/563), 2.5% (225/8870) and 1.1% (6/566) of patients using 60 mg, 30 mg and 15 mg lansoprazole per day respectively. Headache was significantly more often reported by 30 mg users compared to 15 mg users (OR (95% CI): 2.4 (1.1-5.5).

Eventually, 226 cases and 442 matched controls were identified from all lansoprazole users. In Table 1 the distribution of characteristics among cases and controls is shown as well as the crude odds ratio for each characteristic. Adjusted odds ratios were calculated through conditional logistic regression with each possible co-factor included in the logistic model. It was found that female sex (adjusted OR (95% CI): 1.6 (1.1-2.3)) and the reporting of other adverse events (adjusted OR (95% CI): 2.5 (1.7-3.6)) were significantly associated with the reporting of headache. Cases reported more frequently (53.5% versus 32.8%) other adverse events and on average more (1.8 versus 1.5) other adverse events as compared to controls. The most frequently (> 5%) reported adverse events were all reported more often in cases compared to controls, namely dizziness (15.9% versus 2.9%), nausea (13.3% versus 4.5%), diarrhoea (11.9% versus 7.0%), abdominal pain (8.0% versus 3.2%) and flatulence/gas pain/belching (6.6% versus 2.7%).

Table 1
Distribution of characteristics among cases and matched controls

	Cases		Controls			
	N=226	%	N=442	%	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Women	137	60.6	224	50.7	1.5 (1.1-2.2)	1.6 (1.1-2.3)
Age (years)						
0-30	12	5.3	19	4.3	(reference)	(reference)
30-45	48	21.2	92	20.8	0.8 (0.4-1.7)	0.6 (0.3-1.5)
45-60	83	36.7	148	33.5	0.8 (0.4-1.8)	0.7 (0.3-1.5)
60-75	71	31.4	135	30.5	0.8 (0.4-1.7)	0.6 (0.3-1.4)
> 75	12	5.3	48	10.9	0.3 (0.1-0.8)	0.2 (0.1-0.6)
Smoking	54	23.9	115	26.0	0.9 (0.6-1.3)	0.9 (0.6-1.3)
Unknown	0	0.0	1	0.2		
Alcohol consumption	106	46.9	213	48.2	0.9 (0.7-1.3)	1.1 (0.7-1.6)
Unknown	0	0.0	1	0.2		
Daily dose of lansoprazole						
≤ 30 mg	211	93.4	407	92.1	(reference)	(reference)
≥ 60 mg	15	6.6	35	7.9	0.8 (0.3-1.7)	0.9 (0.4-2.1)
First use of lansoprazole	194	85.8	376	85.1	0.9 (0.5-1.6)	0.9 (0.5-1.7)
Indication of lansoprazole therapy						
GERD	147	65.0	267	60.4	1.3 (0.9-1.9)	1.3 (0.8-2.0)
Ulcer	30	13.3	57	12.9	1.1 (0.6-1.8)	1.2 (0.7-2.3)
Co-morbidity	84	37.2	164	37.1	1.0 (0.7-1.4)	1.0 (0.7-1.5)
Any other adverse event reported	121	53.5	145	32.8	2.5 (1.7-3.5)	2.5 (1.7-3.6)

* adjusted by conditional logistic regression for each possible co-factor

An age of 75 years or more was significantly less often documented in cases in contrast to controls (adjusted OR (95% CI): 0.2 (0.1-0.6)). Smoking habits, alcohol intake, prescribed lansoprazole dose and first use of lansoprazole seemed to be well balanced between cases and controls. No differences were found between the groups regarding the indication for lansoprazole use. Lansoprazole therapy was prescribed for the eradication of *Helicobacter pylori* in 4.0% of the cases versus 6.4% of the controls. Co-morbidity (excluding acid related diseases) was documented in 37.2% and 37.1% of the cases and the controls respectively. The profile of co-morbidity was similar for both groups of patients. Of all cases and controls 54.0% and 53.6% respectively were evaluated by specialists.
For a total of 170 cases and 317 controls in a ratio of 1:1 or 1:2 medication histories were retrieved. Table 2 shows a higher current use of analgesics and NSAIDs in cases compared to controls.

Table 2
Current and past co-medication among cases and matched controls

	Cases		Controls			
	N=226	%	N=442	%	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
Current drug use*						
Any cardiovascular drug	32	18.8	67	21.1	0.8 (0.5-1.3)	0.6 (0.3-1.5)
Benzodiazepines	24	14.1	46	14.5	1.0 (0.5-1.7)	0.9 (0.4-2.3)
Oral antibiotics	21	12.4	47	14.8	0.8 (0.4-1.6)	0.7 (0.4-1.6)
Analgesics	19	11.2	27	8.5	1.7 (0.9-3.4)	1.4 (0.5-3.6)
NSAIDs	9	5.3	13	4.1	1.4 (0.5-3.5)	1.8 (0.5-5.6)
Past co-medication**						
Any cardiovascular drug	28	16.5	51	16.1	0.9 (0.5-1.5)	1.4 (0.5-3.5)
Benzodiazepines	28	16.5	41	12.9	1.3 (0.7-2.3)	1.6 (0.7-3.6)
Oral antibiotics	12	7.1	42	13.2	0.5 (0.2-0.9)	0.4 (0.2-0.9)
Analgesics	26	15.3	35	11.0	1.3 (0.7-2.4)	0.9 (0.4-2.0)
NSAIDs	16	9.4	37	11.7	0.8 (0.4-1.6)	0.6 (0.3-1.6)

* current drug use: drug use at the moment of onset of headache

** past co-medication: drug use during six months prior to the onset of headache

† adjusted by conditional logistic regression for variables mentioned in Table 2

Analysis of co-medication in the 6 months preceding the use of lansoprazole showed a slightly higher use of benzodiazepines and analgesics in cases. Due to the limited numbers, these differences between cases and controls in current and past drug use were not statistically significant.

Regarding cardiac medications, current use of beta-blocking drugs was, not significantly, more habitual in 9.4% of cases as compared to 7.6% of controls (unadjusted OR (95% CI): 1.2 (0.6-2.5). We found that past use of oral antibiotics was less frequent in cases as compared with controls. This association was significant after adjusting for all variables mentioned in Table 1 (adjusted OR (95% CI): 0.4 (0.2-0.9).

In addition, from a subset of 33 cases and 36 controls supplementary questionnaires were completed (Table 3). The headache was predominantly mild (50.4%) or moderate (35.8%) in severity. An association with the study drug was described most commonly as either probable (29.7%) or possible (55.7%). In 54.5% no action was taken due to the headache, whereas a dose reduction of lansoprazole was reported in 6.1% and a discontinuation in 39.3%. The time of onset of the headache was in 42.4% within 2 hours and in 54.5% beyond 2 hours after intake of lansoprazole. Headaches were predominantly present during the day (63.6%), bilaterally located (81.8%) and described as oppressive (69.7%) with accompanying signs and/or symptoms as preference for rest (66.7%) and a negative impact on daily activities (54.5%). Based upon the above mentioned characteristics the headaches could be classified as tension headache (21/33, 63.6%), migraine with/without aura (8/33, 24.2%) and not classifiable headache (4/33, 12.1%).

Of all 25 patients having ceased lansoprazole treatment during the follow-up period, 48.0% (12/25) reported a discontinuation of headache, 32.0% (8/25) a reduction of headache and 20.0% (5/25) no effect. Two patients restarted lansoprazole treatment after a discontinuation leading to the occurrence of the same headache as before.

Previous episodes of headache were documented in 36.4% of the cases (12/33) and 22.2% of the control patients (8/36) (unadjusted OR (95% CI): 2.0(0.6-6.6). The classification of the headache was in 10 out of the 12 cases the same during lansoprazole use as before. Use of analgesics during the three months prior to the

start of the lansoprazole treatment was frequent in cases (n=14, 42.4%) and documented less frequently but significantly (n=4, 11.1%) in control patients (unadjusted OR (95% CI): 5.9 (1.5-25.1).

Table 3
Characteristics of headache during lansoprazole intake

	N=33	%
Onset of headache		
< 2 hours after intake lansoprazole	14	42.4
> 2 hours after intake lansoprazole	18	54.5
Unknown	1	3.0
Headache mainly present		
In morning	2	6.1
During the day	21	63.6
In the evening	2	6.1
Otherwise	8	24.2
Severity of headache		
Mild	13	39.4
Moderate	8	24.2
Severe	2	6.1
Association of headache with lansoprazole		
Unlikely	5	15.2
Possible	18	54.5
Probable	10	30.3
Location headache		
Unilateral	5	15.2
Bilateral	27	81.8
Unknown	1	3.0
Type of headache		
Beating	5	15.2
Oppressive	23	69.7
Otherwise	5	15.2

Table 3
(continued) Characteristics of headache during lansoprazole

	N=33	%
Accompanying signs/ymptoms		
Aggravation of head. during exercise	13	39.4
Restlessness during headache	6	18.2
Preferring resting during headache	22	66.7
Negative effect on daily activities	18	54.5
Nausea or vomiting	8	24.2
Sensitive for light/noise	7	21.2
Classification of headache		
Tension headache	21	63.6
Migraine with/without aura	8	24.2
Not classifiable	4	12.1
Action taken		
None	18	54.5
Discontinuation of lansoprazole	13	39.3
Dose reduction of lansoprazole	2	6.1
Other action	0	0

The intake of alcohol and caffeine was more frequently reduced in cases as controls. Four cases had reduced or stopped intake of alcohol and/or caffeine. Of the controls, one patient reduced alcohol intake and increased caffeine intake, whereas another control increased caffeine intake while alcohol intake was unchanged.

DISCUSSION

The aim of this study was to investigate the incidence and characteristics of headache and to identify the value of co-factors associated with headache in naturally occurring lansoprazole users. Data were used from a large prospective follow-up study in 10,008 lansoprazole users in daily clinical practice incorporating patients with different indications, co-morbidity and the use of co-medication. The incidence density of headache was 7.2 per 1,000 person-years of lansoprazole use and comparable with other observational data stating 4.6 per 1000 per-

son-years [8]. Our frequency of patients reporting headache was relatively low (2.5%), compared to the frequency reported in clinical trials with lansoprazole (3.8-8.8%) [1, 2, 14]. This frequency was significantly dose related. In observational studies, as ours, a general underreporting of adverse events can be expected as compared to clinical trials with follow-up visits required by protocol instead of visits occurring in daily clinical practice. Therefore, we feel that our data more closely represents the natural frequency of headache in lansoprazole users than data from selected patients in clinical trials.

From literature little is known about characteristics of headache during lansoprazole use We found that based upon the reported characteristics the headaches could be classified as tension headache (21/33, 63.6%), migraine with/without aura (8/33, 24.2%) and not classifiable headache (4/33, 12.1%). This pattern resembles the situation in the general population where tension headache represents 72.3% of all recurrent headaches [19].

Among headache patients as compared to lansoprazole users not reporting headache, there were significantly more women. The association with gender is consistent with data from clinical trial literature stating a frequency of 5.6% in women and 4.5% in men using lansoprazole [3]. In clinical trials headache was reported in 8.4% of patients using 60 mg lansoprazole and in 3.8% of patients using 30 mg [3]. Patients with an age of 75 years or more were at a lower risk to develop headache during lansoprazole therapy, a phenomenon also identified in the general population where older age groups showed lower prevalences of headache [11, 20].

The number of patients with other adverse events and the average number of adverse events were considerably higher in patients reporting headache compared to patients reporting no headache. Patients with headache reported diarrhoea, nausea and dizziness significantly more often. All these adverse events are known as common adverse events related with the use of PPIs in general [3-5]. An explanation is that there exists a group of patients who report adverse events more readily. Another explanation is that certain combinations of gastrointestinal and neurological adverse events may occur together in users of PPIs. However, no clinical evidence of this has been published. An association with co-morbidity could not be established, although described in literature [20, 21].

Past use of analgesics was significantly more frequent in patients with headache during lansoprazole use. It is known that in the general population, unrelated to the use of lansoprazole, headache is associated with non-prescription analgesic use. Headache sufferers often use analgesic drugs [22, 23].

In conclusion, the incidence density of headache was comparable with other observational data. The type of headache was in two out of three patients classifiable as tension headache. The analysis of co-factors revealed that women and patients with a history of use of analgesics were at risk to develop headache during lansoprazole use. These co-factors are both well-known co-factors associated with the occurrence of headache in the general population [10, 20]. We additionally found that the reporting of other adverse events was associated with the occurrence of headache during lansoprazole use. A de-challenge of lansoprazole therapy resulted in a cessation or reduction of the headache in 20 out of 25 patients. This together with the existing dose relationship made the association with the drug intake very plausible.

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Chapter 5.3

Characteristics of diarrhoea in 10,008 users of lansoprazole in daily practice: which co-factors contribute?

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SUMMARY

Background: Diarrhoea is one of the most frequently reported adverse events during proton pump inhibitor (PPI) use in any setting. Because of the limited available information, this study was set up with the aim to assess the incidence and characteristics of diarrhoea and to investigate possible associated co-factors in PPI users in daily practice.
Methods: Data were used from a prospective, observational study in which 10,008 lansprazole users were followed over time (1994-1998). The study was designed according to the SAMM guidelines. A nested case-control design was used to compare PPI users reporting diarrhoea with PPI users reporting no diarrhoea.
Results: The frequency of diarrhoea was 3.7% and the incidence density 10.7 per 1,000 patient months of PPI use. The diarrhoea was most commonly loose and occurred on average 4.4 times per day. The analysis of co-factors revealed that patients with concomitant use of oral antibiotics and patients reporting several adverse events, were at risk to develop diarrhoea during PPI use. A de-challenge was positive in 38 out of 48 patients and a re-challenge in 4 out of 4.
Conclusions: In conclusion, diarrhoea was as frequently reported in our study as compared with clinical trials and observational data of lansoprazole users. Besides alcohol use, we found the concomitant use of oral antibiotics and the reporting of certain other adverse events to be associated with the reporting of diarrhoea during lansoprazole use. Although a relationship with the PPI intake seemed very plausible, we suggest that use of alcohol and/or oral antibiotics as a cause of diarrhoea must be taken into consideration in lansoprazole users.

INTRODUCTION

Lansoprazole is a PPI introduced on the Dutch market at the end of 1993 indicated for the treatment of reflux oesophagitis and healing of gastric and duodenal ulcers. At the time of introduction, lansoprazole had been evaluated in several thousands of patients enrolled in clinical trials [1]. Diarrhoea was one of the most common adverse events reported in clinical trials with PPIs, namely in 3.0-3.5% of patients using 30 mg lansoprazole, 1.9-3.7% using 20 to 40 mg omeprazole, 1.5% using 40 to 120 mg of pantoprazole and 2.0-3.0% using 10 to 20 mg rabeprazole [1-4]. In patients with an age of 65 years or more a frequency of diarrhoea of 4.7% is documented [1]. During long-term treatment, diarrhoea occurred in 1.9% to 5% of lansoprazole users compared to 3% of omeprazole users [1]. Besides clinical trial data, estimates of the 'real-world' safety profile are more important but until now scarce [5]. In the PEM study, diarrhoea had the second highest Incidence Density of 9.9 and 4.0 per 1,000 patient months of exposure during respectively lansoprazole and omeprazole use [6]. Furthermore, little is known about the characteristics of diarrhoea as an adverse event during lansoprazole use, such as the severity, consistency, colour, accompanying symptoms, onset and contribution to dosage changes.

One hypothesis behind the occurrence of diarrhoea during lansoprazole use is that the high degree of acid suppression achieved by PPIs may lead to bacterial contamination of the upper gut resulting in diarrhoea by various mechanisms [7-9]. Especially in the elderly, in whom acid reducing drugs are commonly prescribed, this may be of particular importance [10]. Several studies indicated that short term PPI treatment increased bacterial colonisation, whereas long term inhibition of gastric acid did not lead to small intestinal bacterial overgrowth [9-11].

Furthermore, the existence of co-factors has to be taken into account. Possible co-factors associated with the occurrence of diarrhoea may be all diseases involving the osmotic load, the secretion into the intestinal lumen, failure of ion absorption and/or an altered intestinal motility [12]. PPIs are frequently used in combination with other drugs to eradicate *Helicobacter pylori* (*H. pylori).* Most of those regimens have diarrhoea as a commonly reported adverse event [13-15]. An analysis of co-factors such as the use of certain substances (e.g. magnesium salts, theofylline, caffeine, laxatives) and present co-morbidity (e.g. infections,

irritable bowel syndrome and inflammatory diseases) may lead to identification of patients at risk of developing diarrhoea while taking lansoprazole. Therefore, this study was set up to investigate characteristics of diarrhoea and to identify the value of co-factors associated with diarrhoea in daily practice of lansoprazole users, including patients of any age with various indications and underlying diseases. Data were used from a large epidemiological prospective follow-up study of lansoprazole users in daily clinical practice in The Netherlands [16].

MATERIALS AND METHODS

Design

A prospective, observational follow-up study was carried out in 10,008 naturally occurring users of lansoprazole in the Netherlands during the first four years after marketing in the fall of 1993 [16]. The study design included a clear separation in time between the prescribing of the drug and the inclusion of the patient in the study in order to minimise the influence of the study on prescribing behaviour, according to the SAMM guidelines [17]. The overall design has been described in detail elsewhere [16].

Data were analysed according to a nested matched case-control design with a 1:1 or 1:2 ratio for cases and controls. Retrospectively, cases were defined as lansoprazole users reporting diarrhoea as an adverse event. The preceding patient of the same evaluating physician, not reporting diarrhoea during the total follow-up period, was taken as the matched control, this was done in order to limit observer bias [18]. In case the so-defined preceding control patient was not available, the next available patient of the same physician served as the control.

Patients

All patients having used or currently using lansoprazole were included in the study at the first visit or any later follow-up visit after lansoprazole was prescribed. Patients agreed to participate by giving their free informed consent allowing access to all relevant clinical and medication data and storage and analyses of these data. No inclusion or exclusion criteria were applied other than the use of the study drug, meaning that every lansoprazole user independent of indication could enter the study.

Measurements

Data were collected at the inclusion visit and at each follow-up visit during lansoprazole therapy with a maximum follow-up of two years. The data collection was designed not to influence normal procedures. General characteristics such as age, gender, alcohol intake, smoking, specialism of evaluating physician, indication, daily dose of lansoprazole therapy and co-morbidity were recorded.

All (adverse) events whether considered associated or not with lansoprazole therapy were documented. The severity of the adverse events was reported as perceived by the physician and classified as mild, moderate, severe or unknown. The association of the adverse event with the use of lansoprazole as assessed by the physician was documented and coded as unlikely, possible, probable or unknown. Where the same event occurred more than once in one patient, only the first episode was used in the calculations. More than one event in the same class could be coded for one patient.

In addition, for lansoprazole users reporting diarrhoea from January 1996 onwards, as well as for the preceding patient of the same physician, supplementary questionnaires were completed. We received 114 completed questionnaires (response 114/274, 41.62%), making 48 valid cases and controls (48/114, 42.1%). Besides any history of gastrointestinal surgery, detailed information on episodes of diarrhoea three months before lansoprazole therapy and during lansoprazole therapy were documented. This information included consistency, colour, frequency, duration, onset, accompanying symptoms (i.e. abdominal pain, blood, mucus, fever), the effect of fasting, action taken (e.g. discontinuation, restart of lansoprazole therapy), effects of action on diarrhoea, diarrhoea in environment and the question if the patient had been abroad in the last three months.

Analysis

Current drug use was determined as drug use at the moment of onset of diarrhoea, whereas past drug use was defined as drug use during the six months prior to the onset of diarrhoea. For each control without diarrhoea the moment of onset of diarrhoea of the matched case was used as a reference date to estimate current and past use of co-medication and current doses.

Results were tabulated in absolute values and percentages. Baseline comparisons were calculated using crude and adjusted odds ratios with a confidence interval of 95%. Adjusted odds ratios were calculated using conditional logistic regression. Incidence densities were calculated during follow-up as the number of reported adverse events per 1,000 patient months of exposure. The exposure period was defined as the period from the start of therapy until the end of lansoprazole therapy or the end of follow-up when still on therapy. Statistical significance was assumed at p-value < 0.05. All statistical analyses were performed using SAS and EGRET statistical packages.

RESULTS

In this study, data were used from 10,008 lansoprazole users with the aim to assess the incidence and characteristics of diarrhoea and to identify the value of cofactors associated with diarrhoea in daily practice. Diarrhoea was the most frequently reported adverse event in 3.7% of the patients, the incidence density was 10.7 per 1,000 months of exposure. The reporting of diarrhoea was dose related, although not significantly. Diarrhoea was reported in 5.0% (28/563), 3.7% (325/8870) and 2.5% (14/566) of patients using ≥ 60 mg, 30 mg and ≤ 15 mg lansoprazole respectively per day (p=0.08).

All cases with diarrhoea (n=368) were compared with patients not reporting diarrhoea during lansoprazole therapy and evaluated by the same physician according to a nested matched case-control design with a 1:1 or 1:2 ratio for cases and controls. For 346 cases one or two matched control patients were available resulting in 675 matched controls. Of 22 cases no matched control patient was available.

The results of this matched case-control analysis are shown in Table 1. The Odds Ratios are adjusted by conditional logistic regression for sex, age, smoking, drinking, dose, indication, any other adverse event and any other co-morbidity.
Specialists evaluated 52.9% of all patients, while 47.1% was seen by a general practitioner. There were no significant differences in gender, age, smoking and prescribed daily doses between cases and controls. Alcohol consumption was reported slightly more frequently in cases compared to controls (adjusted OR (95% CI): 1.5 (1.1-2.1)). Cases frequently had more ulcers compared to controls (adjusted OR (95% CI): 1.5 (1.1-2.1)).

Table 1
General characteristics of diarrhoea cases and matched controls

	Cases		Controls		Crude OR	Adjusted OR
	N=346	%	N=675	%	(95% CI)	(95% CI)
Women	193	55.8	363	53.8	1.1 (0.8-1.4)	1.2 (0.9-1.6)
Age (years)						
0-30	19	5.5	42	6.2	(reference)	(reference)
30-45	57	16.5	131	19.4	1.0 (0.5-1.8)	0.9 (0.5-1.8)
45-60	103	29.8	205	30.4	1.1 (0.6-2.0)	1.1 (0.6-1.9)
60-75	120	34.7	217	32.2	1.3 (0.7-2.3)	1.3 (0.7-2.3)
> 75	47	13.6	80	11.9	1.4 (0.7-2.7)	1.4 (0.7-2.8)
Smoking	89	25.7	189	28.0	0.9 (0.7-1.2)	0.9 (0.7-1.2)
Unknown	1	0.3	0	0		
Alcohol consumption	184	53.2	310	45.9	1.4 (1.0-1.8)	1.5 (1.1-2.1)
Daily PPI dose						
≤ 30 mg	317	91.6	628	93.0	(reference)	(reference)
≥ 60 mg	29	8.4	47	7.0	1.3 (0.7-2.2)	1.4 (0.7-2.8)
Indication of therapy						
GERD	215	62.1	426	63.1	0.9 (0.7-1.3)	0.9 (0.7-1.2)
Ulcer	47	13.6	94	13.9	1.0 (0.7-1.5)	1.5 (1.1-2.1)
H. pylori eradication	47	13.6	59	8.7	2.7 (1.6-4.6)	1.4 (0.8-2.5)
Other adverse event(s)	134	38.7	172	25.5	1.9 (1.4-2.6)	0.9 (0.6-1.3)
Other gastrointestinal	81	23.4	84	12.4	2.2 (1.5-3.1)	1.3 (0.7-2.6)
Neurological	45	13.0	51	7.6	1.8 (1.2-2.9)	2.1 (1.5-3.0)
Dermatological	12	3.5	25	3.7	0.9 (0.4-1.8)	1.6 (1.0-2.5)
General	11	3.2	13	1.9	1.7 (0.7-4.1)	0.8 (0.4-1.8)
Co-morbidity (excl. acid)	134	38.7	257	38.1	1.0 (0.8-1.4)	0.9 (0.6-1.4)
Cardiovascular	61	17.6	99	14.7	1.2 (0.9-1.8)	0.8 (0.5-1.3)
Gastrointestinal	41	11.8	76	11.3	1.1 (0.7-1.6)	1.1 (0.7-1.6)
Endocrine	27	7.8	44	6.5	1.2 (0.7-2.1)	1.0 (0.6-1.5)
Musculoskeletal	19	5.5	24	3.6	1.6 (0.9-3.0)	1.2 (0.7-2.0)

Lansoprazole therapy as part of a *H. pylori* eradication regimen was more common in cases than in controls. However the difference was not significant (adjusted OR (95% CI): 1.4 (0.8-2.5)). Of all cases 38.7% reported one or more other adverse events compared to 25.5% of the controls (adjusted OR (95% CI): 0.9 (0.6-1.3)). Neurological adverse events (adjusted OR (95% CI): 2.1 (1.5-3.0)) and dermatological adverse events (adjusted OR (95% CI): 1.6 (1.0-2.5)) were reported significantly more frequently by cases. Co-morbidity seemed to be well balanced between cases and controls.

Table 2
Co-medication among diarrhoea cases and matched controls

	Cases		Controls		Crude OR	Adjusted OR
	N=255	%	N=473	%	(95% CI)	(95% CI)
Current drug use*						
Cardiovascular drugs	43	16.9	95	20.1	0.8 (0.5-1.2)	0.4 (0.2-0.8)
- Beta-blocking drugs	15	5.9	40	8.5	0.6 (0.3-1.2)	0.3 (0.1-0.9)
- Ace-inhibitors	8	3.1	14	3.0	1.2 (0.5-3.0)	0.9 (0.1-6.8)
Benzodiazepines	17	6.7	37	7.8	0.9 (0.5-1.6)	0.9 (0.4-2.0)
Oral antibiotics	14	5.5	11	2.3	2.6 (1.1-6.4)	2.7 (1.0-6.9)
Analgesics	9	3.5	18	3.8	0.8 (0.3-2.0)	1.0 (0.4-2.7)
NSAIDs	7	2.7	11	2.3	1.2 (0.4-3.4)	1.2 (0.4-3.9)
Antidiarrhoea drugs	4	1.6	4	0.8	3.0 (0.5-17.0)	2.5 (0.4-15.8)
Past co-medication**						
Cardiovascular drugs	62	24.3	100	21.1	1.1 (0.7-1.7)	1.2 (0.7-2.0)
- Beta-blocking drugs	25	9.8	41	8.7	1.2 (0.8-1.7)	2.1 (1.1-3.9)
- Ace-inhibitors	9	3.5	15	3.2	1.0 (0.6-1.7)	1.8 (0.8-4.1)
Benzodiazepines	45	17.6	82	17.3	1.2 (0.5-3.1)	1.6 (0.2-12.2)
Oral antibiotics	54	21.2	114	24.1	1.0 (0.6-1.4)	1.0 (0.6-1.6)
Analgesics	26	10.2	63	13.3	0.7 (0.4-1.1)	0.5 (0.3-0.9)
NSAIDs	32	12.5	60	12.7	1.1 (0.6-1.8)	1.0 (0.6-1.8)
Antidiarrhoea drugs	3	1.2	8	1.7	0.7 (0.2-3.0)	0.5 (0.1-2.4)

* current drug use: drug use at the moment of onset of diarrhoea

** past co-medication: drug use during six months prior to the onset of diarrhoea

For a total of 255 cases and 473 controls in a ratio of 1:1 or 1:2 medication histories were retrieved. Results are shown in Table 2. The Odds Ratios are adjusted by conditional logistic regression for sex, age, smoking, drinking, dose, indication, any other adverse event and any other co-morbidity. Table 2 shows a higher current use of oral antibiotics in cases compared to controls (adjusted OR (95% CI): 2.7 (1.0-6.9), while cardiovascular drug use was less frequent in cases (adjusted OR (95% CI): 0.4 (0.2-0.8). Analysis of co-medication in the 6 months preceding the use of lansoprazole showed a slightly higher use of beta-blocking drugs in cases (adjusted OR (95% CI): 2.1 (1.1-3.9) and a little lower use of analgesics in cases (adjusted OR (95% CI): 0.5 (0.3-0.9).

Of a subset of 48 of the 368 patients reporting diarrhoea and 48 matched patients reporting no diarrhoea additional information was collected. The pattern of general characteristics between the 48 cases and controls was similar with the pattern given in Table 1.

As can be seen in Table 3, according to the physician the severity of the diarrhoea in the 48 cases was most frequently either mild (39.6%) or moderate (39.6%), whereas 20.8% was characterised as severe. As assessed by the physician, 45.8% was possibly and 35.4% probably related to the lansoprazole exposure. The diarrhoea was most frequently loose (66.7%), followed by watery (31.3%) or alternately loose and watery (2.1%). The colour was lighter compared to normal in 54.2% of cases, in 39.6% of equal colour and in the remaining cases (6.3%) darker. The diarrhoea occurred with a mean frequency of 4.4 times per day (min. 1, max. 16 times) and continued for 11.7 days as a mean (min. 2, max. 42 days). Accompanying symptoms were abdominal pain/cramps (41.7%), mucus (12.5%), fever (2.1%) and/or blood (2.1%). None of the cases had been abroad during the three months preceding the onset of diarrhoea and only one case reported the occurrence of diarrhoea in his environment. Of all cases, 87.5% (42/48) had no previous episode of diarrhoea three months before starting lansoprazole, compared to 95.8% (46/48) of the controls. All those previous episodes of diarrhoea included loose stools. Of four cases the diarrhoea might be explained by present co-morbidity. One case was known with Irritable Bowel Syndrome in combination with diverticulitis, one with Irritable Bowel Syndrome, one with a history of alcohol abuse and one with hypertension in combination with diabetes mellitus. None of the controls had co-morbidity.

Table 3
General characteristics of diarrhoea during lansoprazole intake

	N=48	%
Severity of diarrhoea		
Mild	19	39.6
Moderate	19	39.6
Severe	10	20.8
Association of adverse event with lansoprazole		
Unlikely	9	18.8
Possible	22	45.8
Probable	17	35.4
Consistency of diarrhoea		
Watery	15	31.3
Loose	32	66.7
Alternately watery/Loose	1	2.1
Color compared to normal faeces		
Lighter	26	54.2
Darker	3	6.3
Equal	19	39.6
Accompanying symptoms		
Abdominal pain / cramps	20	41.7
Mucus	6	12.5
Blood	1	2.1
Fever	1	2.1
Diarrhoea reason for discontinuation lansoprazole	23	47.9

All six cases reporting episodes of diarrhoea preceding and during lansoprazole treatment noted that the diarrhoea during lansoprazole use was in general the same as that prior to lansoprazole use (regarding consistency, colour, frequency per day, accompanying symptoms). Discontinuation of therapy led to a cessation of the diarrhoea in only one of the six patients. In 47.9% (23/48) of the cases lansoprazole therapy was discontinued because of the diarrhoea, leading to a dis-

continuation of the diarrhoea in 69.6% (16/23) of cases, a reduction of the diarrhoea in 8.7% (2/23) and no effect in 17.4% (4/23) of the cases (one patient unknown). In addition, 52.1% (25/48) of the patients ceased lansoprazole treatment for other reasons and the diarrhoea discontinued in 64.0% (16/25), reduced in 16.0% (4/25) and continued in 16.0% (4/25) of the patients (one patient unknown). In four patients with a discontinuation of the diarrhoea after stopping therapy due to diarrhoea, lansoprazole treatment was restarted and all four reported the re-occurrence of the same diarrhoea without blood, mucus and/or fever. These four patients were not familiar with diarrhoea in the past.

DISCUSSION

The main objective of this study was to investigate characteristics of diarrhoea and to identify the value of co-factors associated with diarrhoea in lansoprazole users in daily practice.

Data were used from a large prospective, observational follow-up study in 10,008 lansoprazole users in Dutch daily practice [16]. Diarrhoea was the most frequently reported adverse event in 3.7% of the patients, the incidence density was 10.7 per 1,000 months of exposure. The frequency was comparable with results from clinical trials with lansoprazole stating frequencies of 3.0-3.5% [7, 8]. The incidence density was similar with available information stating an incidence density of 9.9 from observational studies [5].

The case control analyses revealed no differences in age, gender, smoking behaviour, daily lansoprazole dose and co-morbidity among patients reporting diarrhoea compared to patients reporting no diarrhoea. Cases used alcohol or oral antibiotics significantly more frequently compared to controls. Excessive consumption of alcohol may be associated with increased gastrointestinal symptoms, such as diarrhoea [19]. In addition, patients reporting diarrhoea recognised significantly more other adverse events compared to the control patients, especially neurological and dermatological events. Lansoprazole therapy as part of a *H. pylori* eradication regimen was more common in cases than in controls, although not significantly. So in these patients, as well as in patients with the indication ulcers, the diarrhoea might be caused partly through the use of one of the other prescribed medicines [13-15]. This is also demonstrated by the higher current use of oral antibiotics.

In this study we investigated 48 patients reporting diarrhoea during lansoprazole use in detail. As assessed by the physician, 81.2% of the onset of diarrhoea was possibly or probably related with lansoprazole use and 60.4% was moderate or severe. The consistency was most frequently loose (66.7%), commonly accompanied by abdominal pain/cramps (41.7%), the colour lighter then normal faeces (54.2%) and occurred on average 4.4 times a day. The diarrhoea was in 47.9% of cases the reason to discontinue lansoprazole treatment. Previous episodes of diarrhoea in the three months preceding the intake of lansoprazole were infrequent in cases and controls. If present, these episodes were not related with lansoprazole use, and could frequently be explained by present co-morbidity.

Of all patients with diarrhoea, any discontinuation of lansoprazole treatment led to a cessation or reduction of the diarrhoea in 79.2% (38/48). So, at least a probable association between the onset of diarrhoea and lansoprazole therapy was confirmed in nearly four out of five patients with diarrhoea. Excluding patients with previous episodes of diarrhoea led to the same figures (78.6%, 33 of 42). In four of the patients renewed lansoprazole intake reinitiated the diarrhoea, which confirmed a definite relationship between the intake of lansoprazole and the occurrence of diarrhoea.

In conclusion, diarrhoea is as frequently reported in our study as in clinical trials and observational studies with lansoprazole. A probable relationship between the occurrence of the diarrhoea and the use of lansoprazole was identified. A rechallenge was positive for all four tested patients. Besides alcohol use, concomitant antibiotic use and the reporting of other adverse events, no other co-factors could be found which were associated with the onset of diarrhoea during lansoprazole use. Although a relationship with the PPI intake seemed plausible, we suggest that use of alcohol or antibiotics as a cause of diarrhoea must also be taken into consideration in these patients.

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Chapter 6

Summary and discussion

SUMMARY AND DISCUSSION

At the start of this thesis we have underlined the importance of drug safety as a key topic in the evaluation of drug therapy outcomes. Due to the fact that drug prescribing, the characteristics of drug users, and drug taking behaviour in real life may be different compared to clinical trials, there is a continuous need to monitor and evaluate what drugs do when they are used in routine daily clinical practice [1-3]. In the choice of an appropriate study design to do so, several scenarios are feasible [4-6]. Essentially, one may choose out of field studies and automated database studies [2]. The limitations of automated databases are widely discussed in the literature [2, 7]. In case one wants to study the effects of the early use of a new drug in the market, field studies may be the strategy of choice because many databases have the inherited disadvantage of lack of relevant clinical and lifestyle data, variability of prescribing leading to small numbers and selected patterns of early prescriptions, and a lag time between the moment of drug prescribing and availability of the data [5, 8].

The development of strategies for building field cohorts of recipients of a new drug looks promising. However, such strategies are by nature very costly and time consuming, and represent a risk of seeding pressure in the form of driving prescriptions, in particular when the pharmaceutical industry is sponsoring the research. The establishment of European guidelines for Safety Assessment of Marketed Medicines (SAMM) in 1994 has been a major progress in improving scientific standards and postmarketing surveillance practices [9]. In this context, the initiative was taken to set up a postmarketing study (named 'Peptic Survey') directly after the introduction of the proton pump inhibitor (PPI) lansoprazole to the Dutch market in the fall of 1993. In total 4-years of follow-up data was collected in order to evaluate patterns of use, safety and effectiveness of this new compound in naturally occurring groups of patients in the Netherlands (1994-1998). In this thesis, background, concept and results of this study are presented and discussed.

Response to PPI therapy

Major methodological aspects as well as the main results of the follow-up study are captured in Chapter 2. Chapter 2.1 describes the design of a prospective, open label, observational follow-up study. The design incorporated five of the six rec-

ommendations of the European SAMM guidelines [9]. So a population as representative as possible of the general population was followed over time, the design was non-interventional and there was a clear separation in time between the prescribing of the drug and the inclusion of the patient in the study. Physicians could include as stipulated in the protocol a maximum number of patients per two years follow-up time. All Dutch general practitioners (GPs), internists and gastroenterologists were approached with the request to participate. In order to avoid inclusion bias, participating physicians and pharmacists were remunerated with only a modest fee equivalent to the reimbursement of their time spent to complete the record forms or generate the medication histories. All patients having used or using lansoprazole could be included in the study at the first visit or any later follow-up visit after lansoprazole was prescribed by giving their written informed consent. No further selection criteria or prescribing protocols were applied.

We used the total cohort to make comparisons between groups of different exposure patterns (follow-up design) or between different outcomes (nested case control design). The Medical Ethics Committee of the Utrecht University Medical Centre has approved the protocol. Patients could be identified by an identification code only. All data and documents related to patients were kept in strict confidence and in accordance with the official privacy regulations. Data were collected at the inclusion visit and at each follow-up visit during lansoprazole therapy, with a maximum follow-up of two years, by reviewing the medical file and by patient questionnaire. The data collection aimed not to influence normal procedures in any way. No additional diagnostic tests were requested from the physician regarding the diagnosis and measurement of patient outcomes. Medical data were recorded by participating physicians, while pharmacists provided drug dispensing records related to the study patients. Data-entry, -validation and -analyses were performed by an independent Contract Research Organisation.

Additionally, the overall results of the first 5,669 evaluated patients included by 374 GPs and 117 specialists regarding the safety, effectiveness and patterns of daily use were given in this chapter.

We found that the patterns of use of lansoprazole in daily practice deviated from the recommendations given in the patient information leaflet. The drug was also used in patients for the treatment of ‘gastritis’, ‘dyspepsia’, ‘duodenitis’, and the

eradication of *Helicobacter pylori (H. pylori).* This phenomenon has also been reported by Bashford et al; in 1998 they found that 46% of new PPI prescriptions were outside the licensed indications [10]. Furthermore, we noticed that PPIs were also prescribed in 60 mg dosage regimens, in a few pregnant women and in complicated patients with co-morbidity and co-medication.

Nevertheless, lansoprazole was found to be safe in this naturally occurring group of users. Specific patient groups were identified with a higher risk to develop adverse events. The profile of lansoprazole users reporting adverse events could be characterised by females, moderate alcohol users, concomitant OTC-users, and patients with the presence of co-morbidity. With this information, patients can be better instructed and informed about the occurrence of adverse events while using lansoprazole [11].

Effectiveness appeared to be comparable to results found in clinical trials in the registered indications for lansoprazole. The effectiveness found in our study was high, taking into account the fact that patients were only endoscopically examined in 50.3% of patients, that 29% of the patients did not have licensed indications and that patients with complex morbidity were included. We found similar results for the total study group of 10,008 patients, as illustrated in Chapters 2.2 and 5.1.

In Chapter 2.2, we looked at patients not responding appropriately to lansoprazole treatment. As clinical trials usually demonstrate high healing rates of 85-98%, there is growing interest in how non-response to PPI treatment in routine daily clinical practice can be explained and understood [11, 12].

We used a matched nested case-control design to compare non-responding (cases) and responding (controls) lansoprazole users. Non-response was defined as worsening or non-improvement of symptoms at the first evaluation after at least 8 weeks of use, response as disappearance or improvement of symptoms within 8 weeks of use, or at the first evaluation after 8 weeks of use. Controls were matched by evaluating physician. We found that an age of over 60 years, heavy smoking and previous PPI use were strongly associated with non-response. This knowledge that non-response to previous therapy drives non-response may encourage physicians to follow users with previous PPI use more carefully.

Drivers of prescriptions for lansoprazole

Chapter 3 elaborates on the question as to which factors drive the prescription of PPIs. In Chapter 3.1 we considered the association between lansoprazole use and exposure to NSAIDs. It is well known that NSAIDs may induce acid related disorders and that PPIs are used to prevent and treat these acid related disorders in NSAID users [13, 14]. We found that one out of five PPI prescriptions were directly NSAID-related. A history of NSAID was present in 19.4% of all PPI prescriptions, whereas in 1.6% PPIs were prescribed for the reason of prevention. Concomitant use of corticosteroids and/or anticoagulants, as well as female sex and an age between 45 and 75 were revealed to be associated factors for NSAID related PPI use.

In Chapter 3.2 we evaluated the question whether or not physicians are triggered to prescribe a drug more frequently through participation in an industry sponsored postmarketing study, and whether thereby selection bias of patients may occur. Basic characteristics of the postmarketing study group were weighed against data of the population based PHARMO Record Linkage System which provides a reasonably valid reference representing the Dutch market place [15]. Results indicated that physicians participating in the postmarketing study followed one out of eight of all new lansoprazole users in the Netherlands (12.8% based on comparison with PHARMO records). We could not find evidence of excessive prescribing of lansoprazole by participating physicians. Expressed as a rate fraction we calculated that overall 9% of the patients included by the GPs in the study group, were attributable to participation in the study. The basic patient characteristics (i.e. age, gender) of the postmarketing population were quite similar when compared with the profiles of lansoprazole users in the reference population.

We found a slightly higher proportion of prescriptions by medical specialists when compared to GPs. An interesting finding was that patients included in the postmarketing study had less likelihood of being previous users of peptic ulcer drugs (OR (95% CI): 0.6 (0.5-0.7), indicating that there was a greater likelihood of including patients with relatively minor gastrointestinal disorders in the postmarketing surveillance study. Nevertheless, the patterns of a slow increase in time and the relation with the type of prescriber were identical in the reference patients and the postmarketing study.

Helicobacter pylori eradication therapy analyses

In Chapter 4 we investigated *H. pylori* eradication therapies that included lansoprazole. The role of PPIs in the eradication of *H. pylori* have became very important in recent years [11, 16].

Participating physicians provided data on 527 patients treated with lansoprazole as part of *H. pylori* eradication therapy from 1994 until April 1998. According to Dutch and European recommendations developed in 1996-1997, 70 to 75% of the patients had an indication justifying *H. pylori* eradication, as is represented in Chapter 4.1. These findings are consistent with the results of other studies indicating that the majority of prescribers act consistently with current recommendations [17]. In 83.9% of all patients a diagnostic test(s) was used prior to treatment. In line with results of a study performed in a clinical practice setting in the US, a considerable variation in the choice of treatment schedules was found, 22 different drug schedules were prescribed [18]. The triple combinations lansoprazole, clarithromycin and amoxicillin or metronidazole were used most frequently (in 33.6% and 18.4% of all patients respectively). The recommended triple schedules were used in two out of three patients.

In a subset of the population with eradication therapies we were able to reveal data on pre- and post testing of *H. pylori* (N=149). Eradication rates based on the data in this subgroup were as high as 86.6% (129/149) and comparable with the findings of clinical trials [11, 16, 19, 20]. Adverse events were reported in 19.4% of all patients. During the study there was a shift from prescribing dual to (specific) triple schedules, whereas quadruple schedules showed a small increase in use up to 20-30%. In general, GPs were slower in prescribing *H. pylori* eradication therapies compared to specialists, reflecting a more conservative practice style in general practice [21]. In line with this we found that specialists were also more likely to do pre- and post testing of *H. pylori.* The medley of prescribed eradication schedules and the variability of indications of treatments showed that there was ample confusion at the time of the study on how to approach *H. pylori* infections. Today, (inter)national guidelines provide a useful framework for decision making in clinical practice [22]. The justification for post testing is still a matter of discussion [23]. As eradication rates are usually high, the necessity of post eradication confirmation could be of minor importance.

Chapter 4.2 examined continued use of PPIs following *H. pylori* eradication. Therapies combining antibiotics and PPIs have shown to be effective in clinical trials to eradicate *H. pylori* in peptic ulcer patients. Triple and quadruple therapies provide the highest eradication rates of >90%, while for dual therapies overall eradication rates with a maximum of 60-80% are commonly accepted [11, 16, 18-20]. We evaluated restarting treatment with PPIs after eradication was completed and found that 41.1% of patients indeed did. The occurrence of GERD in the diagnosis could be an explaining factor, but even in one out of three peptic ulcer patients without GERD and treated with triple or quadruple therapies, we found continuation of PPI treatment. So far, there is no evidence that eradication schemes including lansoprazole as PPI are less efficacious. Additional research is necessary to investigate the impact of non-compliance and possibly other determinants on continued PPI use.

Safety of PPI treatment

Chapter 5 discusses the safety of lansoprazole. In Chapter 5.1 data on the overall safety profile of lansoprazole in daily practice is presented. 805 GPs and 266 specialists included a total of 10,008 lansoprazole users with a broad range of diagnoses. Of all patients, 17.4% reported one or more adverse events. The profile and frequency of reported adverse events was consistent with results from clinical trials and other observational studies [24-27]. The most frequently reported adverse events were diarrhoea, headache, nausea, skin disorders, dizziness and generalised abdominal pain/cramps. Regarding rare adverse events, such as dry mouth, gynaecomastia and blindness/severe vision disorders, we found comparable profiles as described with PPIs in literature [28-34]. Furthermore, no lansoprazole related unlabelled adverse event of any clinical significance was recorded. In line with Weber's theory, we found that the reporting of adverse events related to lansoprazole did not proceed at a uniform rate, higher rates prevailed soon after marketing with a stable lower pattern occurring after two years [35].

In Chapter 5.2, a study is described with the aim to assess the incidence and characteristics of headache and to investigate possible associated co-factors in PPI users in daily practice. In clinical trials, headache is one of the most frequently reported adverse events (frequency 1.3-8.8%), while results of an observational study indicate that headache is the fifth most frequently reported adverse

event (incidence densities 2.5-4.6 per 1,000 patient months of exposure) during PPI use [11, 24-26, 36, 37]. However, there are no specific observational studies performed regarding the occurrence and features of headache during use of PPIs in daily practice. We showed that the frequency of headache was 2.5%. As can be expected, headache was reported less frequently in this study compared to clinical trials with lansoprazole [11]. The incidence density was 7.2 per 1,000 patient months of PPI use and so comparable with other observational data of lansoprazole and omeprazole users [26]. Tension headache was seen in two out of three patients with headaches. Using a matched case-control design, patients reporting headache or not, were compared. Besides several commonly accepted co-factors such as female gender and a history of analgesic use, we also found the reporting of other adverse events to be associated with the reporting of headache during lansoprazole use [38, 39]. Patients with headache also significantly more often reported diarrhoea, nausea and dizziness. The cessation of headache after discontinuation of PPI use and the found dose relationship, suggested that headache was indeed a side-effect of lansoprazole use.

Diarrhoea is also a frequently reported adverse event during PPI use in any setting [24, 25]. Because of the limited information available, a study was set up with the aim to assess the incidence and characteristics of diarrhoea and to investigate possible associated co-factors in PPI users in daily practice [40]. As given in Chapter 5.3, the frequency of diarrhoea was 3.7% and the incidence density 10.7 per 1,000 patient months of PPI use, and comparable with results of clinical trials and observational data of lansoprazole users [11, 24-26]. The diarrhoea was most commonly loose and occurred on average 4.4 times per day. We used a matched nested case-control design to compare patients reporting diarrhoea with patients not reporting diarrhoea. The analysis of co-factors revealed that patients with alcohol use, concomitant use of oral antibiotics and patients reporting several adverse events, were at risk to develop diarrhoea during PPI use. Excessive consumption of alcohol may be associated with increased gastrointestinal symptoms, such as diarrhoea [41]. Lansoprazole therapy as part of a *H. pylori* eradication regimen was in cases more common than in controls, although not significantly. So in these patients, as well as in patients with the indication ulcers, the diarrhoea might be caused partly through the use of one of the other prescribed medicines i.e. antibiotics [42-44]. This is also demonstrated by the higher current use of oral antibiotics. A de-challenge was positive in 80.0% (38/48) and a re-challenge in 100% (4/4). Although a relationship with the PPI intake seemed

very plausible, we suggest that use of alcohol or antibiotics as a cause of diarrhoea must also be taken into consideration in lansoprazole users.

CONCLUSIONS

The series of studies captured in this thesis have one common source, a prospective, open label, follow-up study to evaluate patterns of use, safety and effectiveness of the PPI lansoprazole in a naturally occurring group of patients in the Netherlands (1994-1998). Of a population of over 10,000 patients starting treatment with lansoprazole, data on medical history, co-morbidity, drug use, disease course and clinical follow-up have been collected. Clinical record forms of this cohort have been completed representing in total 35,000 users-months of follow-up. Indeed, a very time consuming and costly operation, resulting in a wealth of data and opportunities to study specific questions related to the postmarketing of a new drug. In this case a PPI: lansoprazole.

The study was designed and performed according to the SAMM guidelines. Briefly, this means basically no in- or exclusion criteria with respect to patient enrolment in the study, a modest remuneration for participating physicians and, most importantly, a separation in time between the moment of prescription of the study drug (i.e. lansoprazole) and the moment of inclusion of the patient in the study in order to avoid seeding prescriptions. By doing so, a large cohort of 10,008 patients was constructed and followed over time. The highest standards of professional conduct and confidentiality were maintained throughout the study. What have we learned from all this?

A primary interest of the study was to evaluate patterns of use of lansoprazole. The drug has been used for a variety of indications, frequently also beyond the official labelling of peptic ulcer and reflux oesophagitis. The study on the seeding of prescriptions revealed that in the limited number of cases when seeding was seen it most likely occurred in patients with relatively minor peptic disorders, including unlicensed indications. One out of five lansoprazole prescriptions was NSAID related. The use of corticosteroids, anticoagulants, female gender and an age between 45 and 70 years were strongly associated with NSAID induced PPI-use. Awareness of the increasing risk to develop acid related disorders during NSAID use has been increased during the study period.

Lansoprazole was used in many different combinations with the aim to eradicate *H. pylori*. The medley of prescribed eradication schedules and the large variety in pre- and post testing for the existence of *H. pylori* confirmed a great need for guidelines and protocols to ensure treatment success. Both international and national guidelines are now in place. It was a peculiar finding that many patients with *H. pylori* eradication continued lansoprazole treatment (41.1%). Even one out of three peptic ulcer patients without GERD and treated with triple or quadruple therapies had continued PPI use after *H. pylori* eradication therapy. This result has been repeatedly found in other studies, and represents an important message for today's pharmacotherapy in not being too optimistic in achieving expected benefits of new therapies.

Regarding safety, we found that 17.4% of all studied patients reported adverse events. No unlabelled events were detected. The profile and frequency of occurrence were analogous to results of clinical trials and other observational studies. The reporting rates of adverse events decreased in time. We found that certain patients had a higher risk to develop adverse events, namely women, alcohol consumers, OTC-users and patients with co-morbidity. The type of headache during PPI use seemed to be most often tension headache and the occurrence was associated with female gender, a history of analgesic use and the tendency of also reporting other adverse events. The onset of diarrhoea during PPI use was related with the reporting of other adverse events, alcohol use and the concomitant use of antibiotics, an important finding for ensuring treatment compliance with *H. pylori* eradication schemes including antibiotics.

The main findings of our observational study were in accordance with the results of clinical trials and observational studies with lansoprazole and other PPIs, both in terms of effectiveness and safety. In addition, we were able to gain more in depth insight into the patterns of use of a new drug launched on the Dutch market. Peptic Survey was designed as a field follow-up study bringing data from various sources (e.g. medical charts, clinical record forms, pharmacy records, patient questionnaires) together in one research database. This approach is most appealing when prescribing of a new drug is highly variable at the moment of product launch in the market place and when drug exposure is not yet sufficiently covered by automated databases. A major concern remains the costs and time burden of building such large cohorts of recipients of a new drug in the market. Industry will continue to play a major role in funding these studies. A critical

appraisal of a possible conflict of interest remains necessary [45]. Fortunately, some recent examples of such cohort studies, both field and database driven, have shown the feasibility of achieving an acceptable balance of industry and scientific interests in conducting postmarketing research [46-49]. The post-marketing project described in this thesis certainly does not represent a panacea for solving all problems, but has surely contributed to the knowledge base of conducting sound postmarketing studies of new drugs.

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Samenvatting

SAMENVATTING

In hoofdstuk 1 van dit proefschrift hebben we het grote belang van de veiligheid van geneesmiddelen bij het evalueren van geneesmiddelengebruik onderstreept. Het voorschrijven van geneesmiddelen, de kenmerken van de gebruikers en de wijze van gebruik kunnen in de dagelijkse klinische praktijk afwijken van de situatie in klinisch onderzoek. Daarom is er continu behoefte aan het bewaken en evalueren van hetgeen geneesmiddelen doen in de dagelijkse klinische praktijk. Er zijn verschillende scenario's met betrekking tot de opzet van een onderzoek toepasbaar.

Men kan kiezen tussen veldonderzoek en onderzoek met geautomatiseerde gegevensbestanden. De beperkingen van onderzoek met geautomatiseerde gegevensbestanden zijn uitgebreid beschreven in de literatuur. Indien men onderzoek wil doen naar de effecten van het eerste gebruik van een recent op de markt geïntroduceerd geneesmiddel heeft veldonderzoek de voorkeur. Geautomatiseerde gegevensbestanden hebben namelijk als nadeel dat belangrijke klinische gegevens ontbreken, dat door de grote variatie in voorschrijven er sprake is van kleine aantallen en geselecteerde vroege voorschriften en er een vertraging is tussen het moment van voorschrijven en de beschikbaarheid van de gegevens.

De ontwikkeling van methoden voor de opzet van veldonderzoek met groepen gebruikers van nieuwe geneesmiddelen lijkt veelbelovend. Echter, deze methoden zijn van nature kostbaar, nemen veel tijd in beslag en met name bij onderzoek dat door de farmaceutische industrie wordt gesponsord kan dit leiden tot een stimulatie van het voorschrijven, ook wel 'seeding' genoemd. De totstandkoming van Europese richtlijnen voor het vaststellen van de veiligheid van geregistreerde geneesmiddelen (SAMM) in 1994 heeft een grote bijdrage geleverd in het verbeteren van wetenschappelijke standaarden en de praktijk van postmarketing surveillance. In deze context is het initiatief genomen voor de opzet van de postmarketing studie (genaamd 'Peptic Survey') direct na de introductie van de proton pomp remmer (PPI) lansoprazol in het najaar van 1993. Gedurende 4 jaren zijn (vervolg-)gegevens verzameld ten einde de patronen van gebruik, de veiligheid en de effectiviteit van dit nieuwe geneesmiddel te evalueren bij gebruikers in de dagelijkse klinische praktijk in Nederland (1994-1998). In dit proefschrift worden de achtergronden en resultaten van deze studie weergegeven en bediscussieerd.

Reactie op PPI therapie

De belangrijkste methodologische aspecten alsmede de algemene resultaten van de follow-up studie zijn beschreven in hoofdstuk 2. In hoofdstuk 2.1 wordt de opzet van de prospectieve, open label, observationele follow-up studie weergegeven. In de opzet was rekening gehouden met de Europese SAMM richtlijnen. Dit betekent dat een groep zo representatief als mogelijk voor de algemene populatie was gevolgd in de tijd. De studie was zonder interventies en er was een duidelijke scheiding in de tijd tussen het voorschrijven van het geneesmiddel en de insluiting van de patiënt in de studie. De artsen mochten een bepaald maximum aantal patiënten insluiten per twee jaar follow-up, zoals vermeld in het protocol. Alle Nederlandse huisartsen, internisten en gastro-enterologen werden benaderd voor deelname. Om bias in de deelname te voorkomen, werden de deelnemende artsen en apothekers beloond met een bescheiden bijdrage, een tegemoetkoming voor de tijd nodig voor het invullen van de gegevens of het vervaardigen van de medicatie-overzichten. Alle patiënten die lansoprazol gebruikten of hadden gebruikt konden worden ingesloten in de studie bij het eerste of een volgend bezoek nadat lansoprazol was voorgeschreven en mits schriftelijk toestemming was verkregen. Andere selectie-criteria of voorschrijfprotocollen waren niet van toepassing.

We hebben de totale groep deelnemers gebruikt om vergelijkingen te maken tussen groepen met verschillende blootstellingen (follow-up opzet) en verschillende uitkomsten (genest case-control-onderzoek). De Medisch Ethische Commissie van het Utrecht Universiteit Medisch Centrum had het protocol goedgekeurd. Patiënten konden alleen door een identificatie code worden geïdentificeerd. Alle gegevens en patiënt gerelateerde documenten werden vertrouwelijk behandeld in overeenstemming met de officiële privacy regelgeving. Gegevens werden verzameld tijdens het bezoek waarbij de patiënt in de studie werd ingesloten en de daaropvolgende bezoeken gedurende lansoprazol gebruik met een maximum van twee jaar follow-up. Dit werd gedaan door middel van het bestuderen van de medische status en vragenlijsten voor de patiënt. Het streven was om de normale procedures op geen enkele wijze tijdens de gegevensverzameling te beïnvloeden. De arts werd niet verzocht om extra diagnostische testen uit te voeren voor het vaststellen van de diagnose of de effecten. De medische gegevens werden vastgelegd door de deelnemende artsen, terwijl de apothekers zorg droegen voor de

geneesmiddelenoverzichten van de patiënten. De gegevens werden door een onafhankelijke Contract Research Organisatie ingevoerd in een databestand, gevalideerd en geanalyseerd. In hoofdstuk 2.1 werden verder de algemene resultaten met betrekking tot de veiligheid, effectiviteit en de patronen van dagelijks gebruik getoond van de eerste 5.669 geëvalueerde patiënten die door 374 huisartsen en 117 specialisten waren ingesloten. We zagen dat de patronen van lansoprazol gebruik afweken van de aanbevelingen in de IB1-tekst. Het geneesmiddel werd namelijk ook gebruikt voor de behandeling van 'gastritis', 'dyspepsia', 'duodenitis', en de eradicatie van *Helicobacter pylori (H. pylori)*. Verder registreerden we voorschriften van lansoprazol in een dosis van 60 mg, bij een aantal zwangere vrouwen en bij gecompliceerde patiënten met co-morbiditeit en gebruik van comedicatie. Desondanks bleek lansoprazol bij deze groep gebruikers in de dagelijkse klinische praktijk veilig. Er werden specifieke patiënten groepen geïdentificeerd met een groter risico voor het optreden van bijwerkingen. Lansoprazol gebruikers die bijwerkingen rapporteerden waren vrouwen, matig alcohol gebruikers, gelijktijdig OTC gebruikers en patiënten met co-morbiditeit. Met de verkregen informatie kunnen patiënten beter worden geïnstrueerd en voorgelicht over het optreden van bijwerkingen tijdens lansoprazol gebruik. De effectiviteit bleek vergelijkbaar met de resultaten gevonden in klinisch onderzoek bij de geregistreerde indicaties. De effectiviteit in onze studie was hoog, met name gezien het feit dat slechts 50.3% endoscopisch was onderzocht, dat 29% van de patiënten een indicatie buiten de geregistreerde indicaties had en dat patiënten met complexe morbiditeit ingesloten waren. We vonden dezelfde resultaten voor de totale groep van 10.008 patiënten, zoals weergegeven in hoofdstukken 2.2 en 5.1.

In hoofdstuk 2.2 keken we naar patiënten die niet adequaat reageerden op de lansoprazol behandeling. Omdat klinisch onderzoek veelal hoge genezingspercentages toont van 85-98%, is er een toenemende interesse hoe het niet-reageren op een PPI behandeling in de dagelijkse klinische praktijk verklaard kan worden. We hebben gebruik gemaakt van een genest case-control-onderzoek met matching om niet-reagerende (cases) en reagerende (controles) gebruikers van lansoprazol te vergelijken. Het niet-reageren was gedefinieerd als het verslechteren of niet verbeteren van de symptomen bij de eerste evaluatie na tenminste 8 weken van behandeling, terwijl reageren was gedefinieerd als het verdwijnen of verbeteren van de symptomen bij de eerste evaluatie binnen 8 weken van behandeling of bij de eerste evaluatie na 8 weken van therapie. Controle patiënten werden 'gematched' op evaluerende arts. We vonden dat een leeftijd boven de 60 jaar, hevig

roken en gebruik van PPI's in het verleden sterk waren geassocieerd met het niet-reageren. Deze kennis dat het niet-reageren op een PPI het niet-reageren stimuleert kan de arts gebruiken bij het zorgvuldig vervolgen van patiënten die al eerder een PPI gebruikten.

Stimuleren van voorschriften van lansoprazol

Hoofdstuk drie gaat in op de vraag welke factoren het voorschrijven van PPI's stimuleren. In hoofdstuk 3.1 wordt de associatie tussen lansoprazol gebruik en de blootstelling aan NSAID's belicht. Het is welbekend dat NSAID's zuurgerelateerde afwijkingen kunnen induceren en dat PPI's worden toegepast bij de preventie en behandeling van deze zuurgerelateerde afwijkingen bij NSAID's gebruikers. We vonden dat één op de vijf PPI voorschriften direct gerelateerd was aan NSAID's. Inductie door NSAID gebruik verklaarde 19,4% van alle PPI voorschriften, terwijl bij 1,6% van alle PPI voorschriften preventie de indicatie van het PPI gebruik was. Gelijktijdig gebruik van corticosteroïden en/of anticoagulantia, het vrouwelijk geslacht en een leeftijd tussen de 45 en 75 bleken factoren te zijn die samenhingen met NSAID gerelateerd PPI gebruik.

In hoofdstuk 3.2 evalueerden we de vraag of artsen aangezet worden tot het voorschrijven van medicatie door deelname aan een door de industrie gesponsorde postmarketing studie en of hierbij selectie-bias van patiënten was opgetreden. Algemene kenmerken van de postmarketing studie groep werden gelegd naast gegevens van het PHARMO Record Linkage System. De resultaten gaven aan dat de artsen die deelnamen aan de postmarketing studie één op de acht (12,8%) van alle nieuwe Nederlandse lansoprazol gebruikers evalueerden. We konden geen aanwijzigingen vinden voor het overmatig voorschrijven van lansoprazol door de deelnemende artsen. We berekenden dat in het algemeen 9% van de door huisartsen ingesloten patiënten kon worden toegeschreven aan de deelname aan de studie. De basale kenmerken van de patiënten van de postmarketing populatie waren vrij vergelijkbaar (bijv. leeftijd, geslacht) met het profiel van de lansoprazol gebruikers in de referentie groep. We vonden een gering groter aandeel voorschriften bij medisch specialisten in vergelijking met huisartsen. Een interessante bevinding was dat onze patiënten de zes maanden voorafgaand aan de postmarketing studie minder vaak geneesmiddelen voor de behandeling van peptische ulcera hadden gebruikt (OR (95% BI): 0,6 (0,5-0,7)). Dit geeft aan dat waarschijnlijk meer patiënten met relatief milde gastro-intestinale afwijkingen in de

postmarketing studie zijn ingesloten. Desondanks waren de patronen van een langzame toename in de tijd en de relatie met het type voorschrijver identiek tussen de referentie groep en de postmarketing studie.

Analyse van Helicobacter pylori eradicatie therapie

In hoofdstuk vier onderzochten we *H. pylori* therapieën waarin ook lansoprazol werd gebruikt. De rol van *H. pylori* en de rol van PPI's bij de eradicatie van *H. pylori* is de afgelopen jaren zeer belangrijk geworden. De deelnemende artsen hebben gegevens verzameld van 527 patiënten die met lansoprazol werden behandeld als onderdeel van een *H. pylori* eradicatie therapie in de periode januari 1994 tot april 1998. Volgens de Nederlandse en Europese aanbevelingen, ontwikkeld in 1996-1997, had 70 tot 75% van de patiënten een indicatie waar een *H. pylori* eradicatie voor nodig was. Dit is weergegeven in hoofdstuk 4.1. In 83,9% van alle patiënten was er een diagnostische test(en) voor aanvang van de behandeling verricht. De triple combinaties lansoprazol, clarithromycine en amoxicilline of metronidazol werden het meest toegepast (respectievelijk in 33,6% en 18,4% van alle patiënten). De aanbevolen triple combinatie werd bij twee van de drie patiënten gebruikt.

In een subgroep van de populatie met een eradicatie therapie hadden we informatie over het testen op *H. pylori* (N=149) voor aanvang of na behandeling. De eradicatiepercentages, uitgaande van de gegevens in deze subgroep, waren hoog met 86,6% (129/149) en vergelijkbaar met de bevindingen uit klinisch onderzoek. Bijwerkingen werden gemeld door 19,4% van alle patiënten. Gedurende de studie was er een verschuiving van voorgeschreven dual naar (specifieke) triple schema's, terwijl quadruple schema's een geringe toename in gebruik van 20-30% lieten zien. In het algemeen liepen de huisartsen achter op de specialisten in het voorschrijven van *H. pylori* eradicatie therapieën. Overeenkomstig vonden we dat specialisten meer geneigd waren om voor aanvang- of na behandeling op de aanwezigheid van *H. pylori* te testen. De variatie in voorgeschreven schema's en de variatie in indicaties voor behandeling lieten ons zien dat er ten tijde van de studie veel verwarring bestond over de wijze waarop *H. pylori* infecties aangepakt diende te worden.

Hoofdstuk 4.2 gaat in op voortdurend gebruik van PPI’s na *H. pylori* eradicatie. Uit klinisch onderzoek is gebleken dat combinatietherapieën van antibiotica met

PPI's effectief zijn voor eradicatie van *H. pylori* bij patiënten met peptische ulcera. Triple en quadruple therapieën hebben de hoogste eradicatie-percentages (>90%), terwijl dual therapieën in het algemeen een eradicatie-percentage van maximaal 60-80% hebben. We hebben gekeken naar een nieuwe behandeling met PPI's na eradicatie en we zagen dit in 41,1% van de patiënten. De diagnose GERD kan hierbij een verklarende factor zijn, maar desondanks vonden we bij één op de drie patiënten met peptische ulcera zonder GERD en behandeld met triple of quadruple schema's, een voortzetting van de PPI behandeling. Tot nu toe is er nog geen aanleiding om te veronderstellen dat eradicatie-schema's waarbij lansoprazol als PPI wordt toegepast minder effectief zijn. Extra onderzoek is noodzakelijk om het effect van non-compliance en andere mogelijke bepalende factoren voor het voortzetten van PPI gebruik te bestuderen.

Veiligheid van PPI behandeling

Hoofdstuk 5 bediscussieert de veiligheid van lansoprazol. In hoofdstuk 5.1 wordt het algemene veiligheidsprofiel van lansoprazol in de dagelijkse klinische praktijk gepresenteerd. 805 huisartsen en 266 specialisten hebben in totaal 10.008 lansoprazol gebruikers ingesloten met een scala aan diagnoses. Van alle patiënten, rapporteerde 17,4% één of meer bijwerkingen. Het profiel en de frequentie van de gerapporteerde bijwerkingen kwam overeen met de resultaten uit klinisch onderzoek en andere observationele studies. De meest frequent gemelde bijwerkingen waren diarree, hoofdpijn, misselijkheid, huidafwijkingen, duizeligheid en algemene buikpijn/buikkrampen. Met betrekking tot zeldzame bijwerkingen, zoals droge mond, gynaecomastie en blindheid/ernstige visus stoornissen, werden er identieke profielen gevonden zoals beschreven in de literatuur over PPI's. Verder werden geen onbekende lansoprazol gerelateerde bijwerkingen van klinisch belang gemeld. Overeenkomstig de theorie van Weber vonden we dat het melden van bijwerkingen, gerelateerd aan lansoprazol, in de loop van het onderzoek veranderde. Direct na marketing waren er relatief meer meldingen terwijl na twee jaar het aantal afnam en stabiliseerde.

In hoofdstuk 5.2, wordt een studie beschreven bij PPI gebruikers in de dagelijkse klinische praktijk met als doel de incidentie en de kenmerken van hoofdpijn te bepalen en mogelijk gerelateerde co-factoren op te sporen. In klinisch onderzoek gedurende PPI gebruik is hoofdpijn één van de meest frequent gerapporteerde bijwerkingen (frequentie 1,3-8,8%), terwijl resultaten van een observationele

studie aangeven dat hoofdpijn de vijfde bijwerking in voorkomen is (incidentiecijfer 2,5-4,6 per 1.000 patiënt maanden van blootstelling). Er zijn echter geen observationele studies uitgevoerd naar het voorkomen en de kenmerken van hoofdpijn bij PPI gebruik in de dagelijkse klinische praktijk. We vonden een frequentie van hoofdpijn van 2,5%. Zoals viel te verwachten, werd hoofdpijn in deze studie minder vaak gemeld dan in klinisch onderzoek met lansoprazol. Het incidentiecijfer was 7,2 per 1.000 patiënt maanden van PPI gebruik en dus vergelijkbaar met gegevens van andere observationele studies met lansoprazol en omeprazol gebruikers. Spanningshoofdpijn werd gezien bij twee van de drie patienten met hoofdpijn en migraine bij de rest. Door gebruik te maken van een case-control-onderzoek met matching, werden patiënten die wel of niet hoofdpijn meldden vergeleken. Naast een aantal bekende co-factoren zoals vrouwelijk geslacht en analgetica-gebruik in het verleden, zagen we dat het melden van andere bijwerkingen geassocieerd was met het rapporteren van hoofdpijn tijdens lansoprazol gebruik. Patiënten met hoofdpijn meldden ook significant vaker diarree, misselijkheid en duizeligheid. Het feit dat de hoofdpijn verdween na het stoppen van het PPI gebruik en de gevonden associatie met de dosis maken aannemelijk dat hoofdpijn inderdaad een bijwerking was van lansoprazol gebruik.

Diarree is een eveneens vaak gemelde bijwerking tijdens PPI gebruik in klinisch en observationeel onderzoek. De beperkt beschikbare informatie hierover was de aanleiding om een studie op te zetten met als doel de incidentie en de kenmerken van diarree vast te stellen en mogelijk gerelateerde co-factoren te onderzoeken bij PPI gebruik in de dagelijkse klinische praktijk. Zoals weergegeven in hoofdstuk 5.3, bedroeg de frequentie van diarree 3,7% en het incidentiecijfer 10,7 per 1.000 patiënt maanden van PPI gebruik. De resultaten zijn vergelijkbaar met de bevindingen bij lansoprazol gebruikers in respectievelijk klinisch en observationeel onderzoek. De diarree was meestal brijig van consistentie en trad gemiddeld 4,4 keer per dag op. We hebben gebruik gemaakt van een genest case-control-onderzoek met matching om patiënten te vergelijken die wel of niet diarree meldden. De analyse van de co-factoren bracht aan het licht dat patiënten die alcohol gebruikten, gelijktijdig orale antibiotica gebruikten en ook andere bijwerkingen meldden, een grotere kans hadden op het ontwikkelen van diarree tijdens PPI gebruik. Excessieve inname van alcohol kan gerelateerd zijn aan een toename in het optreden van gastro-intestinale symptomen zoals diarree. Lansoprazol therapie maakte in cases, alhoewel niet significant, vaker deel uit van een *H. pylori* eradicatie schema in vergelijking met controles. Bij deze patiënten en bij pa-

tiënten met ulcera als indicatie zou de diarree mede veroorzaakt kunnen worden door het gebruik van een van deze voorgeschreven geneesmiddelen. Dit is ook zichtbaar aan het frequenter gebruik van orale antibiotica. De diarree verdween in 80,0% (38/48) bij het stoppen van de lansoprazol therapie en kwam weer terug in 100% (4/4) bij het opnieuw gebruiken van lansoprazol. Alhoewel een relatie met PPI gebruik plausibel leek, raden we aan om het gebruik van alcohol en antibiotica als oorzaak van de diarree in overweging te nemen bij lansoprazol gebruikers.

Appendix I

Invitation letter

This letter was used to inform physicians
about the contents of the project and to invite them to participate.

Utrecht, <date>

Dear colleague,

In September 1993 the proton pump inhibitor Prezal® (lansoprazole) was introduced for the treatment of reflux-oesophagitis and peptic ulcers.

Pharmacoepidemiology is an excellent instrument to evaluate the patterns of use in daily practice and desired and not desired effects of this drug in a large patient population. Janssen-Cilag B.V. and Aventis Pharma B.V. endorse the importance of pharmacoepidemiology and have taken the initiative to conduct such research with Prezal®.

Kendle, a clinical research institute, will coordinate this project in conjunction with the Department of Pharmacoepidemiology and Pharmacotherapy of the University Utrecht.

The project will start in January 1994. The protocol is approved by the Medical Ethics Committee of the Utrecht University Medical Centre and the design follows the guidelines as recently described in literature. This means that only patients already using Prezal® will be invited to participate in the project. We kindly request you to collect a limited number of data of these patients. The results of this project will be reported bi-annually.

We would highly appreciate if you would be willing to participate in this project. In this manner, you can significantly contribute to the collection of data that will give you and your colleague's useful information to ensure justified drug use. A summary of the protocol of this project is enclosed.

You can make known your interest by completing the attached reply form.
Please, do not hesitate to contact me in case of questions.

Kind regards,

Mrs. A. Claessens, MD
Kendle

Encl.

REPLY FORM

Name: -
Function: -
Address: -
Zip code/ City: -
Telephone: -

O Does want to participate in the project Peptic Survey
O Does want to receive additional information of the project Peptic Survey

Date: Signature:

SUMMARY

An open non-randomized retrospective postmarketing surveillance to assess the safety and efficacy and to outline the pattern of daily use of Prezal® in the Netherlands.

Introduction — In September 1993 the proton pump inhibitor Prezal® (lansoprazole) was introduced for the treatment of reflux-oesophagitis and peptic ulcers. Clinical studies demonstrated that with Prezal® healing appears quicker and more often compared with H_2-receptor antagonists. The number of adverse events was limited and the reported events were mild in severity and transient. As usual, these clinical studies are performed in strictly described patient populations of relatively limited size. However, to evaluate the use of Prezal® in daily practice larger groups of patients are necessary.

Objective — To get insight into the pattern of use of Prezal® in daily practice and the desirable and undesirable experiences in a large patient population.

Medication — Prezal® capsules (30 mg lansoprazole per capsule).

Participation — Expected 5,000 – 10,000 patients.

Duration project — At least 2 years.

Procedure — Prezal® will be prescribed in daily practice by a large number of participating General Practitioners and specialists. Patients already using Prezal® and returning to their physician will be verbally and in writing informed about the project.
If patients agree to participate in the project, written informed consent will be obtained. The following data will be collected: demographics, medical history, diagnosis, symptoms, therapy and (un)desirable experiences. Each time the patient visit the physician follow-up data will be gathered once more. The pharmacist of the patient will be requested to generate a medication history list of the patient of the previous 6 months.

Start project — January 1994.

Appendix II

Patient information and informed consent

This information leaflet was handed out to all potential participating patients and the contents were discussed with the physician. If patients agreed to participate their written informed consent was obtained to allow access to all relevant clinical and medication data and storage and analyses of these data.

PATIENT INFORMATION

An open non-randomized retrospective postmarketing surveillance
to assess the safety and efficacy and to outline the pattern
of daily use of Prezal® in the Netherlands.

Your general practitioner or gastro-enterologist / internist informed you about a project concerning Prezal®, coordinated by Kendle, a clinical research institute, associated with the University Utrecht.

In this postmarketing surveillance project desirable and undesirable effects of a new drug will be evaluated in large patient-population. Prezal® has become available on the market recently. The drug is used in patients with reflux-oesophagitis or peptic ulcers.

Up to now, clinical studies, with Prezal® in over 2,000 patients with duodenal ulcers, gastric ulcers and reflux-oesophagitis have demonstrated a more rapid and frequent healing without significant side effects compared to most other acid-suppressants.

Prezal® is well tolerated; the incidence of side effects is comparable with other anti-acids. Gastrointestinal symptoms (diarrhoea 1.3%, constipation 1.0%, abdominal pain 0.5% and nausea 0.6%) and neurological disorders (headache 1.3%, dizziness 1.3%) are the most frequent occurring side effects. Other side effects include skin rash (0.6%) and itch (0.4%). All side effects are mild in severity and transient.

The purpose of this postmarketing surveillance is to gain better informed about the safety and efficacy of Prezal® in large populations. We would like you to participate in this project which means that your physician will request information on your medical history and demographics and will register the symptoms and possible adverse events of the drug.
Co-medication prescribed 6 months prior to the start of the project and during the entire project will be obtained from pharmacy records. This information will be sent to the University of Utrecht, so your physician will not receive this information. At each visit your physician will complete another check-list on the occurrence of adverse events and details about your disease.

You are free to withdraw at any time from further participation, without the need to give reasons and without prejudice to further treatment. All information will be stored and analysed anonymously and will be treated confidentially. Information will only be made available anonymously to authorized representatives from the health authorities and/or sponsor of Prezal®. Any risk of the use of Prezal® is insured by the sponsor providing that you have followed the instructions given by the physician.

If you would like to discuss anything regarding the postmarketing surveillance, you can contact your physician.

Name: Telephone:

WRITTEN INFORMED CONSENT FORM

An open non-randomized retrospective
postmarketing surveillance
to assess the safety and efficacy
and to outline the pattern
of daily use of Prezal®
in the Netherlands.

I am fully informed about the nature and objectives of the postmarketing surveillance and have given free informed consent. I am free to withdraw at any time from further participation, without the need to give reasons and without prejudice to further treatment.

I agree that my physician will request the pharmacy to collect my pharmacy records. I also agree that my medical and pharmacy records will be documented and analysed anonymously.

Patient

Name:

Date: ___ / ___ / ___ Signature:

Physician

Name:

Date: ___ / ___ / ___ Signature:

Identification code:

Dankwoord

DANKWOORD

Vele mensen hebben een bijdrage geleverd aan het tot stand komen van dit proefschrift. Eind 1993 kreeg U-Gene Research (thans Kendle) opdracht tot begeleiding van een groot postmarketing surveillance project in opdracht van Aventis Pharma B.V. en Janssen-Cilag B.V. Ik werd gevraagd voor dit project de coördinatie op mij te nemen. In 1995 stimuleerden Tom Schwarz, Marianne Floor en Bert Leufkens me op basis van dit project een proefschrift te schrijven. Derhalve wil ik op de eerste plaats Tom, Marianne en Bert bedanken voor het initiatief van toen en het vertrouwen dat ze in me stelden. Tijdens het promotietraject veranderde U-Gene Research in Kendle en traden er meer veranderingen op. Echter wat bleef was het vertrouwen in mij en het ter beschikking stellen van tijd voor de afronding van het proefschrift door Ronald Koning en Yvonne van Megen. Ik heb dat zeer op prijs gesteld!

Zoals reeds aangegeven was zonder prof. dr. Bert Leufkens het proefschrift nooit gestart en zeker niet voltooid. Bert, in zijn rol als promotor, was er steeds om wetenschappelijke input en onderbouwingen aan te dragen op het moment dat ik dacht waar zijn we nu eigenlijk mee bezig. Je had initiatieven te over, deels zijn ze uitgevoerd en deels zijn ze van tafel verdwenen. Want eens moet het af zijn. Dank je wel, ik heb je begeleiding als zeer leerzaam en plezierig ervaren.

Als tweede promotor wil ik prof. dr. Cock Lamers bedanken voor het geven van vele adviezen op het gebied van de gastro-enterologie, het en het niet uit het oog verliezen van de realiteit van de data. Ik hoop dat ik je reisschema niet teveel heb verstoord.

Dr. Rob Heerdink was mijn co-promotor en zorgde veelal op de donderdag voor ondersteuning bij de afdeling farmacoepidemiologie en farmacotherapie. Ik was één van je vele dagjes-mensen. Je werd vaak belaagd door e-mail, desondanks had je altijd even tijd voor het geven van advies en was immer in voor koffie en uitwisseling van nieuwtjes op velerlei terrein. Zonder je medewerking waren de analyses in EGRET en de verwerking van de medicatielijsten onmogelijk. Dank je wel voor je adviezen, hulp en de plezierige samenwerking.

Tevens wil ik graag de vele anderen bij de disciplinegroep Farmacoepidemiologie en Farmacotherapie bedanken voor hun interesse en gezelligheid.

Welmoed Meijer is mijn zeer gewaardeerde steun en toeverlaat geweest tijdens het grootste deel van dit project. Je hebt tientallen artsen in het land bezocht. Tijdens beide periodes van zwangerschapsverlof heb je mijn taken met betrekking tot het project waargenomen. Je was altijd bereid en in staat tot medewerking, ook bij moeilijke of weinig inspirerende taken. Heel veel dank.

Ook wil ik graag de vele andere (oud-)collega's van Kendle bedanken voor hun medewerking en betrokkenheid. Met name Audrey, Lotte, Ron, Harm, wederom Welmoed, Cecile, Margot en Anjo voor het bezoeken en instrueren van honderden artsen, Sarah voor het corrigeren van de engelse teksten en Ronald, Indra, Armand, Toon en vele anderen bij de verwerking van de bijna 20.000 evaluatieformulieren en ruim 11.000 medicatielijsten.

Bovendien ben ik de honderden huisartsen en specialisten uit Nederland en de tientallen medewerkers van Aventis Pharma B.V., Janssen-Cilag B.V. erkentelijk die elk op hun eigen wijze een bijdrage hebben geleverd aan de verzameling van gegevens van lansoprazol gebruikers.

Aventis Pharma B.V. en in de eerste fase ook Janssen-Cilag B.V. ben ik zeer veel dank verschuldigd. Jullie initiatief in 1993 tot het opzetten van dit project heeft geleid tot het schrijven van dit proefschrift. Met name Yvonne van Megen, Joop van Oene en Kristelle Nusteling hebben een grote wetenschappelijke bijdrage geleverd. Bedankt voor het steeds maar weer lezen en beoordelen van de manuscripten. De sturing van Marja Pronk door het stellen van deadlines en het organiseren van vele projectteam- en adviesraad vergaderingen was een belangrijke rode draad in het verloop van het project. Gezamenlijk is het gelukt om gegevens van meer dan 10.000 lansoprazol gebruikers te verzamelen.

De adviesraad is alle jaren elke drie maanden trouw bijeengekomen. Onderwerpen als compliance, non respons en seeding waren favoriete thema's. Ook werd er veel gesproken over eten. Te denken valt aan het symposium met de titel 'Food for Thoughts' en aan de culinaire omlijstingen tijdens de adviesraden. Het officiële afscheidsetentje hebben we zodoende zelf bereid in een Kookstudio.

Naast de (co-)promotoren maakte prof. dr. Jacques van Eijk deel uit van de adviesraad. De methodologie stond steeds centraal bij je, zoals de selectie van art-

sen en patiënten en het beschrijven van de data. Je geduld, precisie en altijd snel becommentariëren van de artikelen heb ik zeer gewaardeerd.

Dr. Ron Herings wil ik graag bedanken voor zijn idee dat leidde tot het artikel over NSAID gebruik en voor het gebruik van PHARMO-gegevens voor het manuscript over ‘seeding’.

Ik bedank de leden van de leescommisie prof. dr. A.W. Broekmans, prof. dr. J.Th.M. van Eijk, dr. M.E. Numans, prof. dr. A.J. Porsius en dr. B.H.Ch. Stricker voor de snelle beoordeling van mijn manuscript.

Welmoed Meijer en Roel Franken, bedankt voor jullie aanvaarding van de taak als paranimf. Alvast dank voor jullie begeleiding en ondersteuning bij de promotie.

Mam en Pap, bedankt voor jullie altijd aanwezige vertrouwen in mij en de flexibele hulp variërend van oppassen tot allerlei huis-tuin-en-keuken klusjes.

Joost, de inhoud van het proefschrift is niet jouw terrein. Echter je steun bij het schrijven en afronden van het proefschrift was er alle jaren en was onmisbaar. Koen, Floor en Lotte, jullie komst gedurende het bezig zijn aan dit boekwerk heeft gezorgd voor een aangename maar soms ietwat scheve balans tussen werken en ontspanning. Zullen we dan ook morgen naar de dierentuin gaan of liever naar het zwembad?

CURRICULUM VITAE

Angela Bodewes-Claessens was born on December 17th 1963 in Udenhout, The Netherlands. She attended secondary school at 'Maurick College' in Vught and graduated in 1982 (Gymnasium). In that same year she started her medical study. She obtained her Medical Degree (cum laude) in 1989 at the Erasmus University of Rotterdam. In that same year she started working for 2 years in epidemiological research at the Netherlands Institute of Primary Health Care NIVEL in Utrecht. This position was followed by 2 years in clinical research, where she was involved in a phase III study of contraceptives of a pharmaceutical company in Rotterdam. In 1993, she joined the phase II-IV department of the Contract Research Organization Kendle (formerly U-Gene Research) in Utrecht, as coordinator postmarketing studies / Clinical Trial Manager. In this function she was responsible for the conduct of (inter)national phase II-IV clinical research trials in the field of gastro-enterology (including the Peptic Survey project) and psychiatry. From 1999 onwards, this position is titled Project Manager. Since 1996 on, she also is Drug Safety Officer of Kendle and responsible for the Serious Adverse Event Processing according to the (inter) national requirements of several products worldwide. In 1996, she started to work part-time on this thesis at the Department of Pharmaceoepidemiology and Pharmacotherapy of the Utrecht University. She attended courses on e.g. Epidemiology and Medical Decision making, Clinical Data Management, Pharmaco-economics and (Advanced Methods of) Pharmacoepidemiology.

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