Factors associated with non-response in proton pump inhibitor users: a study of lansoprazole therapy

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Abstract
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 in daily practice and for the reason that resistance to PPIs is scarce, we investigated factors 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 to 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.

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Introduction

In the Netherlands, PPIs are registered for use in patients with gastric ulcer, duodenal ulcer and/or gastro-esophageal reflux disease (GERD). 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 [1-5].

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, 6]. 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 [7]. 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 [8]. 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 (i.e. not listed in the SmPC) and/or unproved diagnosis, in atypical dosages and in complex situations for example, patients with previous therapy, co-morbidity and/or co-medication [9-11]. 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 [12]. Due to the limited knowledge regarding response and non-response to lansoprazole use in daily practice and for the reason that resistance to PPIs is scarce, we investigated factors possibly associated with non-response, such as compliance, diagnosis and response to previous treatment [6].

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). All GPs, internists and gastro-enterologists in The Netherlands were invited to participate in the study. Any lansoprazole user regardless of the indication, prescribing physician or prescribed lansoprazole dosage could be entered in the study by a participating physician. Informed consent was obtained from all patients. No additional in- or exclusion criteria were considered. The aim of the study was to evaluate the safety, efficacy and the patterns of daily use of lansoprazole [7]. 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 who 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.

At first all non-responders (i.e.cases) were detected. In addition, from the same evaluating physician two responders (i.e. controls) entered in the study right before the case were selected. If a so-called preceding patient was not available the first suitable control after the case was selected. If no two control patients were available the case was also not included in the analyses. At the end 186 cases and 372 matched controls were available for the analyses. This matching procedure was followed to limit observer bias by taking a control and case form the same evaluating physician [13]. 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 by the physician at subsequent visits after prescription of lansoprazole by reviewing the medical file and by patient questionnaire. The data collection was designed not to influence normal procedures, meaning that no additional testing was necessary for this study. The following details were recorded for all patients: gender, age, alcohol intake, smoking habits, lansoprazole prescribing physician, evaluating physician, 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, GERD 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 factors 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 factors 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.

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.

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

	Cases N=186	*Controls (%)*	*Crude OR N=372*	*Adjusted OR (%)*	*(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)

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 factors 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 [7]. 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, 14, 15]. Thus, the effectiveness of lansoprazole when used in daily practice was comparably high.

The likelihood that non-response was related to certain factors 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.

Factors 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 [10]. Nevertheless we did not see such an association. Gastrointestinal co-morbidity was also not significant-

ly 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 [16, 17]. 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 [6]. 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. In patients with GERD, increasing the prescribed dosage may overcome the resistance [18].

Another factor that has an effect on the response is the patient compliance, in routine daily practice is that 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 [10, 19]. 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 factors 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 [6]. 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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