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Determinants of Headache in Lansoprazole Users in The Netherlands

Results from a Nested Case-Control Study

Angela A.M.C. Claessens,[1,2] *Eibert R. Heerdink,*[1] *Jacques T.H.M. van Eijk,*[3] *Cornelis B.H.W. Lamers*[4] and *Hubert G.M. Leufkens*[1]

1 Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, The Netherlands
2 Kendle, Utrecht, The Netherlands
3 Department of Medical Sociology, Health Care Studies, Faculty of Medicine, University of Maastricht, Maastricht, The Netherlands
4 Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

Abstract

Objective: During proton pump inhibitor (PPI) use, in clinical trials, headache is one of the most frequently reported adverse events (frequency 1.3 to 8.8%), while results of one observational study indicate that headache is the fifth most frequently reported adverse event (incidence densities 2.5 to 4.6 per 1000 patient-months of exposure). 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.

Design: 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 Safety Assessment of Marketed Medicines guidelines. A nested case-control design was used to compare PPI users reporting headache or not.

Results: The frequency of headache was 2.5% in users of lansoprazole and the incidence density was 7.2 per 1000 patient-months of PPI lansoprazole use. Two-thirds of patients with headache had tension headache and one-third had migraine. 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 discontinuation of PPI therapy resulted in a cessation or reduction of the headache in 80.0% (20 of 25).

Conclusions: As can be expected, headache was reported less frequently in this study compared with clinical trials with lansoprazole. The incidence density was comparable with other observational data of lansoprazole and omeprazole users. 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 an adverse effect of lansoprazole use.

The proton pump inhibitor (PPI) lansoprazole was introduced in The Netherlands in the third quarter 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 to 6.9% of omeprazole users, 3.8 to 8.8% of lansoprazole users, 1.3% of pantoprazole users and 2.4 to 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 with clinical trials.[7] In a prescription-event monitoring (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 1000 patient-months of exposure, respectively.[8] It is still unclear if the occurrence of headache in lansoprazole users affects compliance and/or discontinuation rates. 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 gender, caffeine consumption, co-morbidity (myocardial ischaemia, 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]

Because of the high frequency of headache reporting and the indefinite effects on compliance, 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 lansoprazole users in the general population. Analysis of co-factors associated with the occurrence of headache may lead to identification of patients at risk.

Patients and Methods

Design

The study data were derived from a prospective, open label, follow-up study conducted in The Netherlands in 10 008 users of lansoprazole in the general population during the first 4 years following introduction (January 1994 until April 1998). The study was set up to assess the safety and effectiveness of lansoprazole in a population composed of groups of lansoprazole users and to evaluate the patterns of use of lansoprazole in daily practice. The study design incorporated five of the six recommendations of the European SAMM guidelines (guidelines for company-sponsored Safety Assessment of Marketed Medicines), namely:

1. A population as representative as possible of the general population of users, and not selected;
2. No inclusion or exclusion criteria were considered;
3. The medicinal product was prescribed in the usual manner;
4. Patients were not be prescribed the medicine in order to include them;
5. The decision to prescribe was clearly separated from the decision to include the patient in the study;
6. The protocol stipulated the maximum number of patients to be entered by a single physician.[13,14]

The recommendation to include an appropriate comparator group was not followed. For reasons of efficiency we chose to make use of internal comparisons in the analyses. The study protocol was approved by the Medical Ethical Committee of the Utrecht University Medical Centre.

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. The patients' pharmacist, as part of routine pharmaceutical care, provided the medicines. 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 inclusion 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. The data collection was designed not to influence normal procedures by following routine visits with no preset visit schedule. 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, and possible relationship with lansoprazole use, action taken and outcome. The physician reported severity and association of the events with lansoprazole use as either unlikely, possible or probable.

From January 1996, the study protocol was amended so that lansoprazole users reporting headache from this time onwards completed a questionnaire. At the same time, physicians were requested to complete an equal number of questionnaires for patients not reporting headache while receiving lansoprazole.

The questionnaires implemented from January 1996 were used to collect specific data about characteristics of episodes of headache 3 months prior to and during lansoprazole intake, including frequency, duration, onset, location, type, symptoms as nausea/vomiting, phonophobia/photophobia, aggravation by movement, effect on daily activities. 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.[16]

Complete prescription medication histories were obtained through pharmacy records from 6 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.[17]

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 6 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 (CI) 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 1000 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 lansoprazole users in the general population. The frequency of headache in daily practice of lansoprazole users was 2.5% (246 of 10 008) and the incidence density 7.2 per 1000 patient-months of use.

To a certain degree the reporting of headache showed to be dose related. Headache was reported in 2.7% (15 of 563), 2.5% (225 of 8870) and 1.1% (6 of 566) of patients using lansoprazole 60, 30 and 15 mg/day, respectively. Headache was significantly more often reported by users of lansoprazole 30 mg/day compared with users of 15 mg/day [odds ratio (OR) 2.4; 95% CI 1.1 to 5.5].

From all lansoprazole users, 226 cases and 442 matched controls were identified (no matched controls were available for 20 cases and therefore they were not included in this analysis). In table I 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 gender (adjusted OR 1.6; 95% CI 1.1 to 2.3) and the reporting of other adverse events (adjusted OR 2.5; 95% CI 1.7 to 3.6) were significantly associated with the reporting of headache. Cases reported other adverse effects more frequently than controls (53.5 *vs* 32.8%). The most frequently (>5%) reported adverse events were all reported more often in cases compared with controls, namely dizziness (15.9 *vs* 2.9%), nausea (13.3 *vs* 4.5%), diarrhoea (11.9 *vs* 7.0%), abdominal pain (8.0 *vs* 3.2%) and flatulence/gas pain/belching (6.6 *vs* 2.7%).

Although only applicable for a small number of patients, an age of 75 years or more was significantly less often documented in cases (n = 12) in contrast to controls (n = 48) [adjusted OR 0.2; 95% CI 0.1 to 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 II shows a higher current use of analgesics and nonsteroidal anti-inflammatory drugs in cases compared with controls.

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 β-blockers was more frequently seen in cases compared with controls (9.4 *vs* 7.6%, respectively), but this difference was not significant [unadjusted OR 1.2; 95% CI 0.6 to 2.5). 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 I (adjusted OR 0.4; 95% CI 0.2 to 0.9). β-Blockers are associated with headache, but the relevance of less frequent antibiotic use is unclear.

For the subset of lansoprazole users reporting headache from January 1996 onwards (n = 83), 35 completed questionnaires were received (response rate 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

Table I. Distribution of characteristics among cases and matched controls

	Cases (n = 226)		Controls (n = 442)		Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
	n	%	n	%		
Women	137	60.6	224	50.7	1.5 (1.1-2.2)	1.6 (1.1-2.3)
Age (y)						
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						
≤30mg	211	93.4	407	92.1	(reference)	(reference)
≥60mg	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 for lansoprazole therapy						
GORD	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)

a Adjusted by conditional logistic regression for each possible co-factor.

CI = confidence interval; **GORD** = gastro-oesophageal reflux disease.

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. Completed questionnaires were received from 42 of these controls (response rate 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. This gave a final subset for comparison of 33 cases and 36 controls. Our response rate was comparable with the overall response rate of 53% found in the UK after requesting postmarketing data on new drugs.[18]

Since the response rate of to the questionnaire was rather low (<50%), it is doubtful whether the results are valid for the general population. Nevertheless our results regarding severity, association with study drug, i.e. lansoprazole, action taken due to headache and time of onset of headache in relation to lansoprazole use were similar in the large subset of 226 cases as in the small subset of 33 cases. The headache was predominantly mild (39.4%) or moderate (24.2%) in severity. An association with the study drug was described most commonly as either probable (30.3%) or possible (54.5%). 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

Table II. Current and past co-medication among cases and matched controls

	Cases (n = 226)		Controls (n = 442)		Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
	n	%	n	%		
Current drug use[b]						
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[b]						
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)

a Adjusted by conditional logistic regression for variables mentioned in table II.

b Past co-medication: drug use during 6 months prior to the onset of headache.

CI = confidence interval; **NSAIDs** = nonsteroidal anti-inflammatory drugs.

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 of 33, 63.6%), migraine with/without aura (8 of 33, 24.2%) and not classifiable headache (4 of 33, 12.1%).

Of all 25 of the 33 patients who ceased lansoprazole treatment for any reason during the follow-up period, 48.0% (12 of 25) reported a discontinuation of headache, 32.0% (8 of 25) a reduction of headache and 20.0% (5 of 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 of 33) and 22.2% of the control patients (8 of 36) [unadjusted OR 2.0; 95% CI 0.6 to 6.6]. The classification of the headache was the same during lansoprazole use as before in 10 of the 12 cases. Use of analgesics during the 3 months prior to the start of the lansoprazole treatment was frequent in cases (n = 14, 42.4%) and documented significantly less frequently (n = 4, 11.1%) in control patients (unadjusted OR 5.9; 95% CI 1.5-25.1).

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 lansoprazole users in the general population. 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 1000 person-years of lansoprazole use and comparable with other observational data stating 4.6 per 1000 person-years.[8] Our frequency of patients reporting headache was relatively low (2.5%), compared with the frequency reported in clinical trials with lansoprazole (3.8 to 8.8%).[1,2,14] In observational studies, as ours, a general underreporting of adverse events can be expected as compared with 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 the 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 of 33, 63.6%), migraine with/without aura (8 of 33, 24.2%) and not classifiable headache (4 of 33, 12.1%). This pattern resembles the situation in the general population where tension headache represents 72.3% of all recurrent headaches.[19] The result that 39.3% discontinued lansoprazole intake showed that the occurrence of the adverse event affected the compliance considerably. There was a significant dose relation between the 30 versus 15 mg/day dosage. A discontinuation of intake of lansoprazole leading to a cessation of the headache made a causal relationship even more plausible. Since the chemical difference among the various proton pump inhibitors is quite indistinct, there are no indications that other proton pump inhibitors demonstrate different user profiles.[20] In other words, headache might be related to use of lansoprazole or to use of the entire class of proton pump inhibitors.

Among lansoprazole users reporting headache as compared with 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 headache of 5.6% in women and 4.5% in men using lansoprazole.[3] In clinical trials headache was re-

Table III. Characteristics of headache during lansoprazole intake (n = 33)

	n	%
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
Accompanying signs/symptoms		
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

ported in 8.4% of patients taking lansoprazole 60 mg/day and in 3.8% of patients taking 30 mg/day.[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.[11,21]

The number of patients with other adverse events and the average number of adverse events were considerably higher in patients reporting headache compared with 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.[21,22]

Previous episodes of headaches and past use of analgesics were significantly more frequent in patients reporting headache during lansoprazole use. Both findings might have contributed to the occurrence of headache during lansoprazole as well. It is known that in the general population, unrelated to the use of lansoprazole, headache is associated with non-prescription analgesic use. People with headache often use analgesic drugs.[23,24]

Conclusions

This study confirmed findings from previous studies and in addition intensified our knowledge regarding the occurrence and characteristics of headache in lansoprazole users in daily practice. The exact mechanism of headache in lansoprazole users, if any, remained unclear, but the existence of some determinants was established.

The incidence density of headache was comparable with other observational data. The type of headache in two-thirds of patients was classifiable as tension headache. The impact on the compliance was considerable; nearly 40% of the users discontinued lansoprazole treatment. 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. The cessation of headache after a discontinuation of use of lansoprazole and the observed dose relationship suggested that headache was indeed an averse effect of lansoprazole use (table III).

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Correspondence and offprints: Dr *Angela AMC Claessens*, Bolognalaan 40, Utrecht, 3584 CJ, The Netherlands.
E-mail: claessens.angela@kendle.com