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ORIGINAL REPORT

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

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SUMMARY

Purpose Diarrhoea is one of the most frequently reported adverse events during proton pump inhibitor use in any setting. Because of the limited available information, this study was set up with the aim of assessing the incidence and characteristics of diarrhoea and to investigate possible associated co-factors in proton pump inhibitor 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 proton pump inhibitor users reporting diarrhoea with those reporting no diarrhoea.
Results The frequency of diarrhoea was 3.7% and the incidence density 10.7 per 1000 patient months of proton pump inhibitor 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 neurological and/or dermatological adverse events, were at risk of developing diarrhoea during proton pomp inhibitor use.
Conclusions In conclusion, diarrhoea was as frequently reported in our study as in clinical trials and observational data of lansoprazole users. 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 proton pump inhibitor intake seemed very plausible, we recommend that use of concomitant medicines as a cause of diarrhoea must be taken into consideration in lansoprazole users. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — lansoprazole; proton pump inhibitor; pharmacoepidemiology; safety; adverse events; diarrhoea

INTRODUCTION

Lansoprazole is a proton pump inhibitor 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 proton pump inhibitors, namely in 3.5% of patients using 30 mg lansoprazole, 1.9% using 20 to 40 mg omeprazole, 1.5% using 40 to 120 mg of pantoprazole and 2.4% 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

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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 1000 patient months of exposure during lansoprazole and omeprazole use respectively.[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 proton pump inhibitors may lead to bacterial contamination of the upper gut resulting in diarrhoea by various mechanisms.[7–9] This may be of particular importance especially among the elderly, to whom acid-reducing drugs are commonly prescribed.[10] Several studies indicated that short-term proton pump inhibitor treatment increased bacterial colonization, whereas long-term inhibition of gastric acid did not lead to small intestinal bacterial overgrowth.[9–11]

All diseases involving the osmotic load, the secretion into the intestinal lumen, failure of ion absorption and/or an altered intestinal motility may induce the onset of diarrhoea.[12] In addition, use of co-medication has to be taken into account as a possible co-factor associated with the occurrence of diarrhoea. Proton pump inhibitors are frequently used in combination with other drugs to eradicate *Helicobacter pylori.* Most of those regimens have diarrhoea as a commonly reported adverse event.[13–15] An analysis of all co-medications used may lead to identification of patients at risk of developing diarrhoea while taking lansoprazole. In conclusion, 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, underlying diseases and use of other medicines. 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 4 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 inclusion of the patient in the study in order to minimize the influence of the study on prescribing behaviour, according to the SAMM guidelines.[17] The overall design has been described in detail elsewhere.[16]

For reasons of efficiency we chose to make use of internal comparisons in the analyses. 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. Two preceding patients of the same evaluating physician, not reporting diarrhoea during the total follow-up period, were taken as matched controls, this was done in order to limit observer bias.[18] In case a so-defined preceding control patient was not available, the next available patient of the same physician served as the control. For all cases preferably two controls were selected and otherwise only one control was picked.

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 had been 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 2 years. 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. 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.

The term 'adverse event' covered any undesirable experience including intercurrent events (or diseases), drug reactions and clinical abnormalities or clinically significant laboratory test abnormalities which

occurred during the study. All (adverse) events whether considered associated or not with lansoprazole therapy were documented, by asking the patient the following question: 'Have you had any complaints since your last visit?' If the patient responds 'yes', the symptom, its onset, duration, severity, association to lansoprazole treatment, as well as the measures taken were recorded. 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.

Analysis

Current drug use was determined as any drug use at the moment of onset of diarrhoea, whereas past drug use was defined as any drug use during the 6 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 1000 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 of assessing the incidence and characteristics of diarrhoea and to identify the value of co-factors 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 1000 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 ($p = 0.08$). In nine patients the lansoprazole dose was unknown.

The severity of the diarrhoea was most frequently either mild (44.0%) or moderate (39.4%), whereas 16.3% was characterized as severe and the remainder unknown (0.3%). As assessed by the physician, 12.2% was not, 48.1% possibly and 39.4% probably related to the lansoprazole exposure. In 0.3% of the events the relation was unknown. In a majority of the events (51.6%) no action was taken and in 42.1% the lansoprazole dosage was reduced or discontinued. In 5.7% additional medication was prescribed due to the event and in 0.5% other measures were taken. The onset of the events was soon after start of the therapy, in 16.0% at day 1, in 32.3% at day 2 to 13 and in 35.9% after day 13, while in 35.9% the information was not available.

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, alcohol use, 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)).

Lansoprazole therapy as part of a *Helicobacter 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.

For a total of 255 cases and 473 controls in a ratio of 1 : 1 or 1 : 2, medication histories were retrieved through pharmacy records. Results are shown in Table 2. The odds ratios are adjusted by conditional logistic regression for sex, age, smoking, alcohol use, dose, indication, any other adverse event and any other

Table 1. General characteristics of diarrhoea cases and matched controls

	Cases		Controls		Crude OR (95% CI)	Adjusted OR (95% CI)
	$N = 346$	%	$N = 675$	%		
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 proton pump inhibitor 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)

Table 2. Co-medication among diarrhoea cases and matched controls

	Cases		Controls		Crude OR (95% CI)	Adjusted OR (95% CI)
	$N = 255$	%	$N = 473$	%		
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 6 months prior to the onset of diarrhoea.

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 among cases (adjusted OR (95% CI): 2.1 (1.1–3.9) and a little lower use of analgesics among cases (adjusted OR (95% CI): 0.5 (0.3–0.9).

KEY POINTS

- The incidence and characteristics of diarrhoea and possible associated co-factors in proton pump inhibitor users in daily practice were evaluated by a 4-year observational follow-up study in the Netherlands using a nested case–control design
- The frequency of diarrhoea was 3.7% and the incidence density 10.7 per 1000 patient months of proton pump inhibitor use, being similar to data from clinical trials and observational studies
- We found the concomitant use of alcohol and/or oral antibiotics and the reporting of neurological and/or dermatological adverse events to be associated with the reporting of diarrhoea during lansoprazole use
- We recommend that use of concomitant oral antibiotics as a cause of diarrhoea must be taken into consideration in lansoprazole users

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] The study was set up following the SAMM guidelines in order to minimize the influence of the study on prescribing behaviour. The overall design has been described in detail elsewhere.[17]

Diarrhoea was the most frequently reported adverse event in 3.7% of the patients, the incidence density was 10.7 per 1000 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 to available information stating an incidence density of 9.9 from observational studies.[5] The reporting of diarrhoea was dose related, although not significantly. As assessed by the physician, 87.5% of the onset of diarrhoea was possibly or probably related with lansoprazole use and 55.7% was moderate or severe. In 42.1% of the patients reporting diarrhoea the lansoprazole dosage was reduced or discontinued due to this event.

The case–control analyses revealed no differences in age, gender, smoking behaviour, daily lansoprazole dose and co-morbidity among patients reporting diarrhoea compared to those reporting no diarrhoea. Cases used alcohol and oral antibiotics significantly more frequently compared to controls. It is reported that chronic alcoholics have more frequent and more severe gastrointestinal symptoms such as diarrhoea.[19] In addition, patients reporting diarrhoea recognized significantly more other adverse events compared to the control patients, especially neurological and dermatological events. An explanation is that there exists a group of patients who report adverse events more readily. Another explanation is that certain combinations of adverse events may occur together in users of proton pump inhibitors. However, no clinical evidence of this has been published. Lansoprazole therapy as part of a *Helicobacter 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 conclusion, diarrhoea is as frequently reported in our study as in clinical trials and observational studies with lansoprazole. Apart from 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 proton pump inhibitor 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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REFERENCES

1. Langtry HD, Wilde MI. Lansoprazole. An update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997; **54**: 473–500.
2. Wilde MI, McTavish D. Omeprazole. An update of its pharmacology and therapeutic use in acid-related disorders. *Drugs* 1994; **48**: 91–132.
3. Fitton A, Wiseman L. Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders. *Drugs* 1996; **51**: 460–482.
4. Langtry HD, Markham A. Rabeprazole. A review of its use in acid-related gastrointestinal disorders. *Drugs* 1999; **58**: 725–742.
5. Miwa LJ, Jones JK, Pathiyal A, Hatoum H. Value of epidemiologic studies in determining the true incidence of adverse events. The non-steroidal anti-inflammatory drug story. *Arch Int Med* 1997; **157**: 2129–2136.
6. 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 Safe* 1997; **6**(Suppl. 1): 1–52.
7. Colin-Jones DG. Safety of lansoprazole. *Br J Clin Pract* 1994; **(Suppl. 75)**: 58–66.
8. Colin-Jones DG. Safety of lansoprazole. *Aliment Pharmacol Ther* 1993; **7**(Suppl.): 56–60.
9. Lewis SJ, Franco S, Young G, O'Keefe SJ. Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole. *Aliment Pharmacol Ther* 1996; **10**: 557–561.
10. Pereira SP, Gainsborough N, Dowling RH. Drug-induced hypochlorhydria causes high duodenal bacterial counts in the elderly. *Aliment Pharmacol Ther* 1998; **12**: 99–104.
11. Nelis GF, Engelage AH, Samson G. Does long-term inhibition of gastric acid secretion with omeprazole lead to small intestinal bacterial overgrowth (in Dutch). *Neth J Med* 1994; **45**: 93–100.
12. Weatherall DJ, Ledingham JGG, Warrell DA (eds). *Oxford Textbook of Medicine.* Oxford University Press: Oxford, 1984.
13. Bayerdorffer E, Lind T, Dite P *et al.* Omeprazole, amoxycillin and metronidazole for the cure of *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol* 1999; **11**(Suppl. 2): S19–S22; Discussion S23–S24.
14. Miwa H, Ohkura R, Murai T *et al.* Impact of rabeprazole, a new proton pump inhibitor, in triple therapy for *Helicobacter pylori* infection—comparison with omeprazole and lansoprazole. *Aliment Pharmacol Ther* 1999; **13**: 741–746.
15. Pohle T, Stoll R, Kirchner T *et al.* Eradication of *Helicobacter pylori* with lansoprazole, roxithromycin and metronidazole—an open pilot study. *Aliment Pharmacol Ther* 1998; **12**: 1273–1278.
16. Leufkens H, Claessens A, Heerdink E, Eijk J van, Lamers CBHW. A prospective follow-up study of 5669 users of lansoprazole in daily practice. *Aliment Pharmacol Ther* 1997; **11**: 887–897.
17. Medicines Control Agency, Committee on Safety of Medicines, Royal College of General Practitioners, British Medical Association and Association of the British Pharmaceutical Industry (November 1993). Guidelines for company-sponsored safety assessment of marketed medicines (SAMM). *Br J Clin Pharmacol* 1994; **38**: 95–97.
18. Steenland K, Deddens J. Increased precision using countermatching in nested case–control studies. *Epidemiology* 1997; **8**: 238–242.
19. Fields JZ, Turk A, Durkin M, Ravi NV, Keshavarzian A. Increased gastrointestinal symptoms in chronic alcoholics. *Am J Gastroenterol* 1994; **89**: 382–386.

