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The Pharmacovigilance of Pantoprazole

The Results of Postmarketing Surveillance on 11 541 Patients in England

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Abstract

Objective: To conduct a postmarketing surveillance study involving patients treated with pantoprazole in general practice in the 6-month period following the launch of this drug in November 1996. Prescription-event monitoring (PEM) provides data on a large cohort of patients in 'real life' settings. The aim was to monitor the safety of pantoprazole as used in general practice. It was the third proton pump inhibitor launched in the UK.

Methods: Patients were identified by data from dispensed prescriptions (FP10s) written by general practitioners (GPs) in England for pantoprazole. Green forms were posted to GPs approximately 6 months following the first prescription identified. GPs were asked to list events that occurred during and after treatment. The incidence density of each event was calculated, ranked and the difference between the incidence of each event in the first and subsequent months of exposure was tested by constructing confidence intervals.

Results: Data were collected for 11 541 patients. The major indications for treatment were oesophageal reflux (22.7%) and dyspepsia (16.9%). Of GPs expressing an opinion, 81.9% reported pantoprazole to be effective. GPs reported 107 events as adverse drug reactions. The most frequent reason given for stopping was diarrhoea (106 patients), which corresponded with the adverse event with the highest incidence density.

Conclusion: This PEM study has defined the reported safety profile of pantoprazole as used in general practice in England. The commonest adverse events found in this study have already been reported in the Summary of Product Characteristics.

Prescription-event monitoring (PEM) is a non-interventional, observational cohort method of pharmacovigilance. This paper reports the findings of a pharmacovigilance study in postmarketing surveillance, which yielded useful clinical data for 11 541 patients treated with pantoprazole in general medical practice in the 6-month period following the launch of this drug in November 1996.

Postmarketing surveillance is essential because the safety database on newly licensed drugs is limited by both the number and characteristics of the patients involved in pre-launch clinical studies.[1] The median number of subjects forming the safety database for successful product licences for drugs containing new active substances is only 1528 volunteers and patients.[2]

Pantoprazole is the third of the proton pump inhibitors to be launched in the UK. The first proton

pump inhibitor launched in the UK was omeprazole (1989), followed by lansoprazole (1994) and pantoprazole in 1996. Two further proton pump inhibitors have subsequently entered the market, namely rabeprazole and esomeprazole.

Proton pump inhibitors are highly effective in treating acid-related upper gastrointestinal disease[3,4] and their use is increasing rapidly.[5,6]

There is no reported difference in the efficacy of the proton pump inhibitors,[7-9] but where pantoprazole differs from the other proton pump inhibitors licensed at the time of its launch, is in its lower potential for drug interactions.[10]

During the period of the study, pantoprazole was licensed for the acute management (up to 8 weeks), of benign gastric ulcer, duodenal ulcer and moderate-to-severe reflux oesophagitis.[11] Subsequently (August 1998), 1 year after the conclusion of the study period, pantoprazole received a licence for long-term treatment and maintenance therapy beyond 8 weeks and is now on a par with omeprazole and lansoprazole in this respect.

Methods

Procedure

PEM is an observational cohort technique used to monitor the safety of newly marketed medicines that have been prescribed by general practitioners (GPs) in England. Details of this technique have been previously described.[12] The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Science in collaboration with the WHO.[13] The method of study also complies with the Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians for records based research.[14] PEM is listed in the Multicentre Research Ethics Committee (MREC) guidelines for researchers (Appendix C) as a method of inquiry and survey conducted in the interest of the public, that does not need reference to an ethics committee.

The patients were identified by means of data from the National Health Service prescriptions (FP10s) written by GPs in England. This information was supplied in confidence by the Prescription Pricing Authority (PPA) to the Drug Safety Research Unit (DSRU) for prescriptions written between December 1996 and June 1997 for pantoprazole.

Questionnaires known as 'green forms', were posted to the prescribing GPs usually during the seventh month following the first prescription identified for individual patients by the PPA, to ensure 6 months of observation for each patient. The green form requested information on age, indication for treatment, duration of treatment, whether the treatment was stopped and the reason for stopping. The GPs were also asked to say whether they felt the drug to be effective or not by responding to the question 'was the drug effective'; they were not asked to provide objective evidence of the drug's efficacy. In addition to these questions, the GP was asked to list events that occurred during treatment and after treatment was discontinued, if the drug had been stopped.

An 'event' was defined as including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in clinical values, or any other complaint considered to be of sufficient importance to enter in the patient's notes. The GP was requested to report all events and was also requested to indicate whether he/she felt a particular event might be an adverse drug reaction (ADR) and whether this event had been reported to the UK Committee on Safety of Medicines (CSM).[12]

'Condition improved' was recorded as an event where the indication for treatment had been stated on the green form already. If the indication for treatment was not recorded then 'condition improved' was not recorded as an event, since it was not known to which 'condition' the statement might refer to with any certainty. Events were coded using an hierarchical in-house dictionary, in

conjunction with documented coding conventions. The verbatim terms used by the doctors are coded to 'lower level' terms, which can be grouped under 'higher level' terms within system organ classes. The dictionary is continually updated with new terms added when appropriate.

Only one green form was sent for each patient, and no more than four green forms were sent to any one GP in any month, although if a GP had prescribed for more than four patients in one month, the questionnaires for these patients would be retained and posted subsequently.

Pregnancies

Any patients identified as having received pantoprazole within 3 months of pregnancy or during pregnancy were followed up with a further questionnaire to the GP.

Deaths

If no clear cause of death could be established from the green form, the death certificate was requested from the Office for National Statistics.

Selected Events

All of the event data were examined to detect serious events and events of possible medical interest such as iatrogenic diseases, unlabelled ADRs (not already mentioned in the Summary of Product Characteristics [SPC],[11]) events reported more often than documented in the SPC[11] or events of unknown aetiology. Serious events were defined as those that were fatal, life-threatening, disabling, incapacitating or that resulted in, prolonged hospitalisation.[15]

Those events requiring further investigation were followed up with the reporting GP by a further questionnaire. Follow-up was deemed unnecessary for cases where the event occurred many weeks or months after the treatment stopped, an alternative cause was reported, or the reporting GP had already provided all the information available. These events were then assessed by the clinical research fellow for any association with the use of pantoprazole.

Causality Assessment

The causality assessment used is an in-house procedure, which took into consideration four factors: the temporal relationship, the role of concomitant medications or concurrent illnesses and the effect of dechallenge and rechallenge. Causality assessment was placed into four categories: probable; where there is strong evidence of association such as dechallenge and rechallenge, possible; where there is a temporal association, unlikely, where there is no temporal association or another cause is stated and unassessable where it is not possible to obtain enough information to draw any conclusion. These criteria are generally similar to those included in the WHO definitions.[16] The decision to follow-up an event was based on seriousness of the event and the clinical research fellow's assessment after review of the green form.

Statistical Analysis

All events reported were coded on to the computer using a dictionary arranged in a system-organ classification and then analysed. Only the first report of each event in each patient was used in these calculations.

PEM provides a numerator (the number of reports) and denominator (the number of patient-months of exposure) over a known time frame. The denominator was calculated by adding together the number of days of exposure for each patient in the cohort and dividing this by 30, to give patient-months of exposure. This enables the incidence density for each reported event to be calculated. These were ranked according to the value of the incidence density in the first month (ID_1) to provide a guide to the events that were most frequently reported. The 99% CIs for the difference between the incidence of each event in the first month (ID_1) and the second to sixth months of exposure (ID_2) were constructed to test whether there was a statistically significant difference in the event rates between the two time-periods. A significantly

higher rate in the first month may indicate a possible adverse event associated with starting pantoprazole.[17]

$$ID_1 = \frac{\text{No. of reports of an event during treatment for period t} \times 1000}{\text{No. of patient-months of treatment for period t}}$$

Thus,

$$ID_t = \frac{N_t \times 1000}{D_t}$$

where: N_t = number of reports of an event during treatment for period t, and

$$D_t = \frac{\text{No. of patient-days of treatment for period t}}{30}$$

where t will represent data from the first month of treatment (ID_1) or the second to sixth months of treatment (ID_2).

Results

Cohort Size

There were 28 159 patients identified who had commenced treatment with pantoprazole between December 1996 and June 1997. 28 159 green forms were posted and 12 521 (44.5%) were returned. 980 (7.8%) of the 12 521 returned forms were classified as void: patient no longer registered with doctor (503 forms); blank forms (283); no record of treatment in notes (156); pantoprazole prescribed but not taken (23); patient's doctor moved or retired (8); duplicate green form for patient (7). This gave a final cohort of 11 541 patients on which the subsequent results are based.

Age and Sex

The mean age (±SD) for males was 53.5 (±16.4) years (range 14–97 years) and for females was 58.0 (±16.3) years (range 12–102 years). The age had not been recorded for 1378 patients (11.9%). Overall the mean age (±SD) of the cohort was 55.9

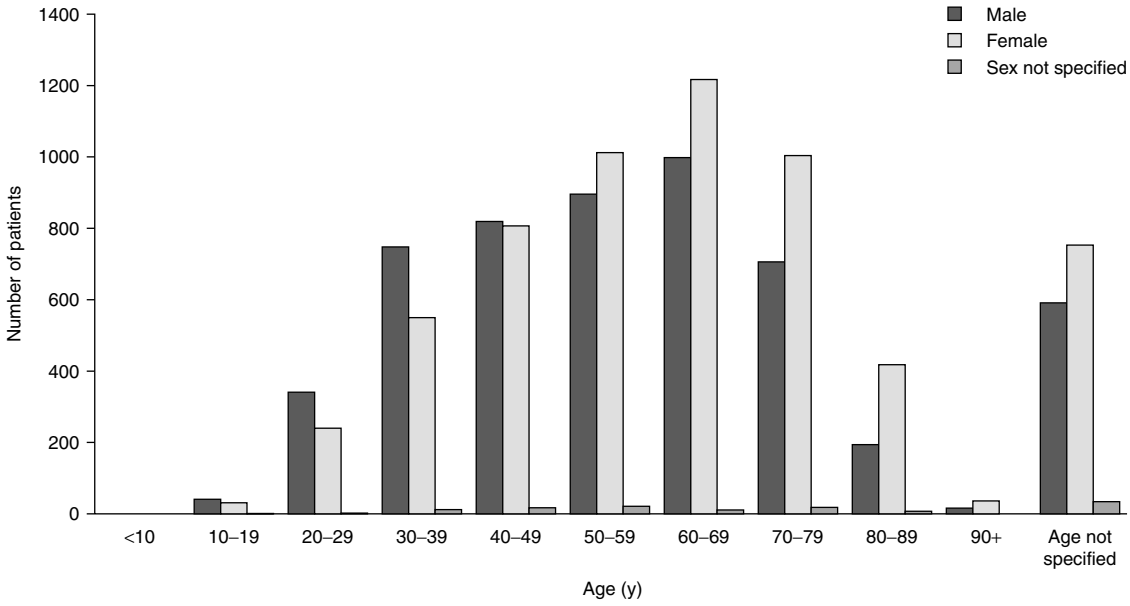

Fig. 1. Age distribution and sex of 11 541 patients.

Table I. Indications for treatment with pantoprazole

Indication	Male		Female		Sex not known		All patients	
	no.	%	no.	%	no.	%[a]	no.	%
Oesophageal reflux	1153	21.6	1451	23.9	18	14.6	2622	22.7
Dyspepsia	917	17.1	1011	16.7	23	18.7	1951	16.9
Pain abdomen	304	5.7	377	6.2	7	5.7	688	6.0
Oesophagitis	310	5.8	337	5.6	7	5.7	654	5.7
Gastritis	181	3.4	161	2.7	3	2.4	345	3.0
Hiatus hernia	123	2.3	214	3.5	1	–	338	2.9
Heartburn	98	1.8	160	2.6	0	–	258	2.2
Duodenal ulcer	123	2.3	81	1.3	4	3.3	208	1.8
Peptic ulcer	71	1.3	40	0.7	2	1.6	113	1.0
Gastric ulcer	40	0.7	35	0.6	1	–	76	0.7
Helicobacter pylori infection	37	0.7	35	0.6	0	–	72	0.6
Barrett's syndrome	43	0.8	26	0.4	0	–	69	0.6
Chest pain	28	0.5	19	0.3	0	–	47	0.4
Prophylaxis	16	0.3	26	0.4	1	–	43	0.4
Duodenitis	21	0.4	21	0.3	0	–	42	0.4
Dysphagia	8	0.1	25	0.4	0	–	33	0.3
Others[b]	117	2.2	106	1.7	3	2.4	226	2.0
Indication not specified	1760	32.9	1943	32.0	53	43.1	3756	32.5
Total	**5350**	**100**	**6068**	**100**	**123**	**100**	**11 541**	**100**

a Percentages <1% not shown.

b Indications each reported in <30 patients.

(±16.5) years (range 12–102 years). The age distribution is given in figure 1.

Of the 11 541 patients, 5350 (46.4%) were males and 6068 (52.6%) were females and sex was not specified in 123 patients (1.1%).

Indications for Use

The major indications for pantoprazole were oesophageal reflux (22.7%) and dyspepsia (16.9%). The indication was not specified for 3756 (32.5%) of the patients. The indications were similar for both sexes (table I).

Duration of Treatment

After six months, 2834 of the 9907 (28.6%) patients for whom it was recorded that treatment was continuing or the date of stopping medication was given, were still being prescribed pantoprazole. In 1634 cases of the 11 541 patients (14.2%) it was not known whether the patient had stopped the drug.

Reported Effectiveness

There were 9289 (80.5%) of 11 541 reports that included an opinion about the effectiveness of pantoprazole.

Pantoprazole was reported by the GPs to have been effective in 7612 (81.9%) of the above cases. This is a subjective evaluation by the GPs that we have not validated and that should not be confused with efficacy, which requires far more robust methods of evaluation.

Adverse Drug Reactions

An event was coded as an ADR if the GP specified on the green form that the event was attributable

to a drug. 107 events in 80 patients were reported by the GPs as ADRs to pantoprazole. Twelve of these 107 (11.2%) events were documented on the green forms as having been reported to the CSM. The most frequently reported ADRs to pantoprazole were diarrhoea in 16 patients and unspecified adverse effects in 13 patients (table II).

Table II. The events most frequently reported as adverse drug reactions (ADRs) to pantoprazole and those reported to the UK Committee on Safety of Medicines (CSM)

Adverse drug reaction		Total	No. reported to CSM
higher level dictionary term	lower level dictionary term		
Diarrhoea		16	0
Unspecified adverse effects		13	0
Nausea/vomiting		12	0
	Nausea	10	0
	Vomiting	2	0
Headache/migraine		10	1
	Headache	10	1
Dizziness		5	0
Malaise/lassitude		4	0
	Malaise	2	0
	Lassitude	2	0
Rash		4	3
Distension abdomen		3	0
Flatulence		3	0
Gastrointestinal unspecified		3	0
Intolerance		3	0
Pain abdomen		3	1
Myalgia		2	1
Oedema		2	1
	Fluid retention	1	0
	Oedema	1	1
Pruritus		2	1
Burning sensation		1	1
Erythema		1	1
Faintness		1	1
Purpura		1	1
Others[a]		18	0
Total		**107**	**12**

a Events each reported in either two or one patient(s).

Reasons for Stopping Pantoprazole

GPs recorded 4754 reasons for stopping pantoprazole for 4415 patients. The most frequently reported adverse events given as the reasons for stopping pantoprazole were diarrhoea (106 cases), nausea/vomiting (77 cases), dyspeptic conditions (60 cases) and headache/migraine (57 cases) [table III].

Event Incidence Densities

For the most frequently reported events, table IV summarises the number of first reports of an event during treatment and the event rates for specified time-periods, the first month of therapy, the second to sixth months of therapy and the total number throughout the treatment period. As stated previously, GPs are not asked whether an event is related to a drug being monitored and so this is a record of the events that occurred during the study period and does not relate to causality. Those clinical events for which the event rates between the two time-periods were significantly different were condition improved, diarrhoea, nausea and vomiting, abdominal pain, hospital referrals with no admission, headache/migraine, dizziness, chest pain/tight chest, noncompliance, malaise/lassitude, intolerance, cholelithiasis/cholecystitis, abdominal distension, and flu-like symptoms. Of these diarrhoea, headache, and dizziness are listed in the SPC as undesirable effects,[11] while others, e.g. abdominal pain, may be associated with the condition being treated and hence are confounded by indication.

Selected Events

Those events that were considered to be of interest after review of the information provided on the green forms were followed up further. Events that as a result of causal assessment by the research fellow were felt to be linked to pantoprazole are listed in table V (i.e. causal assessment was thought to be probable or possible). The causal assessment and whether the event was listed in the SPC are listed in the subsequent columns.

Table III. Reasons for stopping treatment with pantoprazole

Reason for stopping pantoprazole[a]		Number
higher level dictionary term	lower level dictionary term	
Condition improved		2112
Not effective		1056
Non-formulary		213
Effective		110
Diarrhoea		106
Patient request		81
Nausea/vomiting		77
	Nausea	55
	Vomiting	22
Indication for pantoprazole changed		62
Dyspeptic conditions		60
	Dyspepsia	23
	Duodenitis	2
	Gastritis	3
	Heartburn	4
	Barrett's syndrome	2
	Oesophageal reflux	23
	Oesophagitis	3
Noncompliance		59
Endoscopy		58
Headache/migraine		57
	Headache	56
	Migraine	1
Hospital referral unspecified		49
Intolerance		47
Helicobacter		46
Pain abdomen		43
Rash		34
Dizziness		33
Hospital admission, nonsurgical		29
Malaise/lassitude		29
	Malaise	23
	Lassitude	6
Hospital referral, gastrointestinal		27
Gastroscopy		25
Others[a]		341
Total (for all patients where recorded)		**4754**

a Events each reported in <25 patients.

Of the events followed up, the only events that were mentioned in the SPC were rash and headache. Events that were deemed 'probable' by way of rechallenge were one case of rash and one case of paraesthesia. All others were assessed as 'possibly' causally associated but not definitely linked. Only one case required hospital admission and that was purpura, which was also associated with headache and oedema. The patient made a full recovery after stopping the drug. This event had been reported to the CSM.

Gastroenteritis

The event gastroenteritis was looked at specifically because of previous case reports of Campylobacter and salmonellosis associated with other proton pump inhibitors,[18,19] especially in those patients on long-term maintenance therapy. To our knowledge no case reports have been published in relation to pantoprazole so far. Cases where the specific organism had been isolated and those where no specific organism was mentioned, i.e. 'gastroenteritis' was listed as the event, were selected for review. Results can be seen in table VI. Events of nausea/vomiting or diarrhoea, were not included as these could be due to a cause other than infective enteritis. Numbers were too small to make a statistically significant analysis of the data. Just over half (51.5%) of the patients (17 of 33) had stopped taking pantoprazole at the time of the event. While for those who were taking the drug at the time the gastroenteritis occurred, 75% (12 of 16) had been taking it for >28 days.

Deaths

There were 268 deaths reported in the cohort of patients (2.3%) treated with pantoprazole. There were two cases of death where it was not possible to ascertain the cause of death. After review no causes of death appeared to be linked with the use of pantoprazole.

Table IV. Incidence densities per 1000 patient-months of treatment, ranked in order of ID_1, where ID_1 was significantly greater than ID_2

Event	N_1	N_2	ID_1	ID_2	ID_1–ID_2	99%CI		N_A	ID_A
						min	max		
Condition improved	930	1181	101.3	61.5	39.8	30.1	49.5	2219	62.0
Diarrhoea	115	81	12.5	4.2	8.3	5.1	11.6	215	6.0
Nausea, vomiting	95	59	10.3	3.1	7.3	4.3	10.2	169	4.7
Pain abdomen	78	66	8.5	3.4	5.1	2.3	7.8	171	4.8
Hospital referrals no admission	75	93	8.2	4.8	3.3	0.6	6.1	196	5.5
Headache, migraine	72	57	7.8	3.0	4.9	2.3	7.5	132	3.7
Dizziness	48	35	5.2	1.8	3.4	1.3	5.5	85	2.4
Pain chest, tight chest	35	30	3.8	1.6	2.2	0.4	4.1	79	2.2
Noncompliance	35	20	3.8	1.0	2.8	1.0	4.5	61	1.7
Malaise, lassitude	32	25	3.5	1.3	2.2	0.5	3.9	70	2.0
Intolerance	32	12	3.5	0.6	2.9	1.2	4.5	48	1.3
Cholelithiasis, cholecystitis	24	17	2.6	0.9	1.7	0.2	3.2	44	1.2
Distension abdominal	17	8	1.9	0.4	1.4	0.2	2.7	30	0.8
Flu-like symptoms	9	1	1.0	0.1	0.9	0.1	1.8	10	0.3

ID_1 = incidence density for first month; **ID_2** = incidence density for months 2 to 6; **ID_A** = incidence density for each event for the total treatment period; **N_1** = number of events in first month; **N_2** = number of events in months 2 to 6; **N_A** = total number of events.

Pregnancies

There were 10 pregnancies in 10 patients who were exposed to pantoprazole either before or during their pregnancy (table VII).

There were five live normal births, (four where there was initial exposure during first trimester and one where exposure to pantoprazole was uncertain) all born at term and no congenital abnormalities were noted at birth. The baby for whom it was uncertain whether the mother had continued to take pantoprazole during pregnancy, experienced neonatal problems in the first week but these resolved spontaneously and were not felt to be related to pantoprazole after follow up.

Discussion

This was an observational cohort study in which there was no interference with the decision of the GPs regarding which drug to prescribe for their individual patients as patients were identified from dispensed prescriptions.

The study also provided information on the 'real world' use of pantoprazole. The patients were those who were, in everyday clinical practice, prescribed this drug. They were therefore likely to include a wide age range of patients rather than the highly selected patients normally included in clinical studies undertaken for a marketing authorisation application.

The study was of national proportions and was systematic in the sense that all patients for whom National Health Service prescriptions (FP10s) were dispensed in England, during the study collection period, were identified. Collection of prescription data began within 1 month of the drug being marketed to minimise 'survivor' bias.

The study was based upon 'event' monitoring and, therefore, has the potential to identify signals that participating GPs may not suspect to be due to the drug. Not only the pattern but also the frequency of the events reported can be determined, as the duration of treatment is calculated for individual patients.

However, only 12 521 (45%) of the 28 159 green forms that were posted were returned. This response rate was lower than the average response rate for PEM studies (58%) and could conceal possible biases. However, there is no practical method

at present, by which the population of patients whose doctors did return the green forms can be compared with the patient population of those doctors who did not return the forms. If the patients whose GPs failed to return the green forms were different from the patients whose GPs responded, then this difference could have remained undetected. The response rate was nevertheless substantial compared with the proportion of suspected ADRs reported in spontaneous reporting schemes and in other postal surveys to GPs, particularly as GPs are not paid for returning the questionnaires and there is only a single posting of the questionnaires to the GPs.[20-22] The fall in GP response rates to postal surveys and PEM has been reported elsewhere as attributable to increased workload.[23,24] Other methods of improving response to questionnaires such as reminders,[25]and providing feedback[26] are being considered for PEM. The data did not include those patients for whom prescriptions were dispensed by hospitals or on private prescriptions. As with any observational study, it was also not possible to estimate the degree of compliance with the prescribed medication. Furthermore, the quality of the information provided on the green form and follow-up questionnaires depends on the precision of the doctors in reporting these events, imprecision or underreporting of events by GPs are possible sources of bias.

Table V. Events followed up to assess if they were possibly or probably associated with use of pantoprazole. A total of 87 events not including deaths or pregnancies were followed up by a further questionnaire

Event	Total no. followed up[a]	Causal assessment		Mentioned in SPC
		possible	probable	
Rash	4	2	1	Yes
Photosensitive rash	3	1		No
Urticaria	5	3		No
Purpura[b]	1	1		No
Blistering	2	1		No
Myalgia	6	1		No
Joint pain	3	2		No
Abnormal sensation/paraesthesia	3	2	1	No
Balance problems	1	1		No
Headache	2	1	1	Yes
Muscular weakness	1			No
Falls/blackouts	1			No
Epilepsy (new event)	1			No
Disturbance of vision	2			No
Disorders of rhythms	4			No
Vasculitis	1			No
Pancreatitis	3			No
Cirrhosis	3			No
Abnormal LFTs	2			No
Jaundice	8			No
Hypoglycaemia	1			No
Haemopoetic abnormalities	9			No
Laboratory test abnormal	2			No

a Causality assessment could not be undertaken for all events for a variety of reasons, for example: questionnaire not returned; assessed as unlikely to be due to pantoprazole; or there was insufficient information for an assessment.

b Event required hospital admission.

LFTs = liver function tests; **SPC** = summary of product characteristics.

Table VI. Number of gastroenteritis events in relation to the use of pantoprazole and time to onset

Event	Total no. of cases	No. of cases occurring while on treatment	Unknown whether on treatment at time of event	No. of cases occurring after >28 but <56 days of treatment	No. of cases occurring after >56 days of treatment
Campylobacter	7	2		0	1
Gastroenteritis	24	13	1	3	7
Salmonella	1	1		1	0
Giardiasis	1	0		0	0
Total	**33**	**16**	**1**	**4**	**8**

Pantoprazole was thought to be effective by 81.9% of the GPs who offered an opinion on effectiveness. This is a subjective question and is not based on any defined parameters. The most common reasons for stopping pantoprazole and also the most common events on treatment correspond to those events already listed in the SPC: notably diarrhoea, nausea and vomiting, headache dizziness, rash. Other common events were probably confounded by indication, e.g. dyspepsia, abdominal pain, and hospital referral without admission.

Respiratory tract infection appeared as a condition with a high ID_1 but it also has a high ID_2 which indicates that its incidence was relatively common throughout the study period regardless of duration of treatment and so could be assumed to be coincidental to the use of pantoprazole (table IV).

Follow-up of selected events has been reassuring. The only potentially serious event that was linked with pantoprazole was a case of purpura associated with headaches and oedema that resulted in a hospital admission. The patient made a full recovery from this episode once the drug was discontinued and the event was also reported to the CSM by the medical professionals involved.

Gastroenteritis was an event of particular interest given previous published case reports of this event for other proton pump inhibitors,[18,19] but there were insufficient numbers to draw any conclusions.

At the end of month two, 4670 patients were still receiving pantoprazole and at the end of month three, 3768 patients were still taking pantoprazole. This was outside of the recommended licence indications at the time of the study, i.e. >8 weeks. The other proton pump inhibitors at the time already had long-term maintenance therapy indications and this may have influenced some GPs to assume a class effect and so continue prescribing pantoprazole beyond the recommended length of therapy at the time of the study. Pantoprazole did subsequently receive a licence indication for maintenance therapy 1 year after the conclusion of the study.

The SPC also stated that pantoprazole is not recommended in children but did not state any specific age limitations. Thirty-two patients aged

Table VII. Outcomes of pregnancies

Exposure to pantoprazole	No. of pregnancies	Outcomes of pregnancies			
		live births	spontaneous abortion	TOP	not known
Drug stopped before last menstrual period	1	0	0	1	0
Drug initially taken in first trimester	7	4	3	0	0
Exposure uncertain	2	1	0	0	1
Total	**10**	**5**	**3**	**1**	**1**

TOP = therapeutic termination of pregnancy.

between 12 and 17 years received pantoprazole, but there were no reported ADRs to pantoprazole in this age group.

Conclusion

In this PEM study we defined the reported safety profile of pantoprazole as was it used and reported in general practice in England. The majority of events reported in this study were not ADRs and often frequently reported events could be interpreted as a result of confounding due to the recording of symptoms being treated rather than as a result of being treated with the drug. Purpura was one unexpected serious adverse event identified in this study that resulted in admission to hospital. The event had a temporal association since symptoms began with the commencement of therapy and improved after discontinuation of the drug. The most common adverse events, such as diarrhoea, nausea, rash, headache and dizziness found in this study have already been reported in the SPC at the time of this study and the number of deaths gave no reason for concern.

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This study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organizations of Medical Science in collaboration with the World Health Organization.[13] The method of study also complies with the Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians of London.[14] PEM is listed in the Multicentre Research Ethics Committee (MREC) guidelines for researchers (Appendix C) as a method of inquiry and survey conducted in the interest of the public, that does not need reference to an ethics committee.

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