A summary of Food and Drug Administration-reported adverse events and drug interactions occurring during therapy with omeprazole, lansoprazole and pantoprazole

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SUMMARY

Background: Pantoprazole is claimed to have a lower potential for drug interaction than other proton pump inhibitors.

Aim: To estimate the frequency of adverse events and drug interactions reported to the Food and Drug Administration in patients receiving omeprazole, lansoprazole or pantoprazole.

Methods: The study involved a search of the Food and Drug Administration’s database for adverse events and drug interactions with omeprazole, lansoprazole or pantoprazole as primary or secondary suspect drug. An estimate of the amount of drug dispensed during the adverse event collection period (from US drug launch) was obtained from the International Medical Statistics health database.

Results: Of the suspected drug interactions recorded, vitamin K antagonist interactions, although rare, were the most common. The frequency of vitamin K antagonist interactions was 0.09 per million packages for omeprazole and 0.11 per million packages for lansoprazole and pantoprazole. Interactions with benzodiazepines or phenytoin were even rarer, being reported in less than 10 patients on each proton pump inhibitor.

Conclusion: The frequency of reported drug interactions was low for omeprazole, lansoprazole and pantoprazole and vitamin K antagonist interactions were by far the most common. These potentially important drug interactions, although rare, were no less frequent on pantoprazole than on omeprazole or lansoprazole, suggesting a class effect.

INTRODUCTION

The high efficacy of proton pump inhibitors in treating acid-related upper gastrointestinal disease has led to their widespread use. In spite of their excellent safety record, the relative safety of different proton pump inhibitors has been widely publicized over the last few years, with particular emphasis on drug–drug interactions.1–9 It has been suggested that pantoprazole is less likely than omeprazole or lansoprazole to interact with other drugs as a result of minor differences in its metabolic profile.10, 11 In a recent retrospective survey of patient treatment records from US veterans, it was concluded that the co-prescription of omeprazole or lansoprazole with warfarin, clarithromycin or diclofenac led to an increase in adverse events, requirements for care and total costs of care.12 No data on pantoprazole were presented. As we have not previously perceived relevant interaction problems with any of the proton pump inhibitors, we undertook to assess the safety of
pantoprazole in comparison with that of omeprazole and lansoprazole in the clinical setting. Information from a broad database was clearly needed, as many of the recent ‘safety’ comparisons have been conducted in small groups of healthy volunteers and may not be representative of the patient population at large. The evaluation includes overall adverse event data and interactions with other commonly used drugs, with particular emphasis on anticoagulants, obtained from the Food and Drug Administration (FDA) database since the launch of the proton pump inhibitors in the USA.

METHODS

Adverse events reported to the US FDA have been made available by the US FDA through the Freedom of Information Act. Prior to October 1997, the data were coded using COSTART AE terminology and stored by the FDA in the Spontaneous Reporting System. From November 1997 onwards, the data were coded using the MedDRA terminology and stored by the FDA in the Adverse Event Reporting System. In order to combine the data from these two systems, each data set was imported into a relational database utilizing the DB Import application with a schema that mirrored the organization of the original data sets. The FDA provided one-to-one mapping from COSTART preferred terms to MedDRA preferred terms. This was necessary to produce summary frequency tables in the MedDRA format. The interface was modified to support consistent selection of suspect status criteria, and the drug selection screen was modified to allow for the selection of drug names from both data sets. The adverse event database, which was used as the source of information, was compiled directly from the files provided by the FDA release, i.e.

The National Technical Information Service. All cases that contained the names omeprazole, lansoprazole or pantoprazole as primary suspect, secondary suspect or concomitant medication were identified, and, in particular, information on vitamin K antagonist interactions was assembled from the launch of each proton pump inhibitor in the USA (October 1989 for omeprazole, June 1995 for lansoprazole and February 2000 for pantoprazole) to the most recently available reports (September 2001). We did not include rabeprazole in the search because the number of packages sold worldwide (approximately 24 million in 32 countries) since the US launch in August 1999 was too low for a meaningful analysis. The data obtained represent adverse event ‘reporting frequencies’, as opposed to actual overall ‘incidence’, as adverse events are not always reported.

It is important to note that only serious adverse events were reported to the FDA from outside the USA, whereas adverse events reported within the USA were registered as serious and non-serious. The accumulated patient exposure data are based on the total number of packages of drug delivered to pharmacies or hospitals (world-wide) since the launch of each drug in the USA (source: International Medical Statistics health database).

RESULTS

The results of the overall data search are reported in Table 1 and represent all FDA reports received after each drug was launched in the USA (1989 for omeprazole, 1995 for lansoprazole and 2000 for pantoprazole). The drug interactions column represents all events reported in the USA in which the

<table>
<thead>
<tr>
<th>PPI</th>
<th>Date of US launch</th>
<th>Total no. of AEs containing PPI name</th>
<th>Drug interactions where PPI was primary or secondary suspect drug</th>
<th>Most common drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>October 1989</td>
<td>29230</td>
<td>342</td>
<td>AVK† 81 Benzodiazepines 5 Phenytoin 3</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>June 1995</td>
<td>10109</td>
<td>94</td>
<td>21 8 2</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>February 2000</td>
<td>875</td>
<td>12</td>
<td>9 1 1</td>
</tr>
</tbody>
</table>

AE, adverse event; AVK, vitamin K antagonist; FDA, Food and Drug Administration; PPI, proton pump inhibitor.

* World-wide reports to FDA, including serious AEs from outside USA and serious + non-serious AEs from within USA.
† PPI and AVK both labelled as either primary or secondary suspect and a bleeding event or blood abnormality in prothrombin time or international normalized ratio reported.

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proton pump inhibitor was the primary or secondary suspected drug, and one of the events was 'drug interaction' in the MedDRA terminology. This covered interactions with all types of drug. Vitamin K antagonist interactions, although uncommon for all three proton pump inhibitors, constituted the most frequent class in each case. The column for vitamin K antagonist interactions contains data in which, firstly, a vitamin K antagonist was present as a concomitant drug, primary suspect or secondary suspect, and, secondly, one of the events was a bleeding event or an abnormality in prothrombin time or international normalized ratio. Interactions with benzodiazepines and phenytoin, although sometimes perceived as a potential problem, were even less common (Table 1).

In Table 2, the frequency of drug interactions with vitamin K antagonists is expressed per package of drug following the launch in the USA. In addition, the frequency of drug interactions was calculated for the first 19 months after the US launch of each drug, in order to compare frequencies over the same time period from launch.

All cases in which the proton pump inhibitor was the primary suspect in the co-medication and all cases in which the proton pump inhibitor was the sole co-medication are presented. Pantoprazole, as primary suspect drug, was associated with a similar frequency of interactions per dispensed drug package (0.11) as omeprazole (0.08) and the same frequency as lansoprazole. Its interaction frequency as sole co-medication (0.08) was the same as that of omeprazole over the same time interval from launch.

### DISCUSSION

This study provides a comparison of adverse event and interaction data for patients on omeprazole, lansoprazole and pantoprazole, as obtained directly from the FDA database by automated procedures, in order to avoid individual selection bias. The most striking feature of the data is the paucity of events occurring over the time period studied for this widely used class of drug. This confirms the experience of controlled clinical trials and previous adverse event studies which shows that proton pump inhibitors are safe and can be used without safety concerns regarding their potential for interaction.\(^7\), \(^13\)

We concentrated in particular on vitamin K antagonist interactions, as these are reported more frequently than all other interactions combined and are also important from a theoretical perspective.\(^2\), \(^14\) A possible interaction between warfarin and omeprazole was first suggested by a single case report of widespread bruising and haematuria when a patient on warfarin started taking omeprazole.\(^15\) A study in healthy men showed no clinically significant influence of omeprazole on the anticoagulation activity of warfarin, i.e. no changes in warfarin dosing were required.\(^16\) The interaction was further studied in patients in an attempt to gauge its frequency in the clinical environment.\(^17\) The effect of 20 mg/day omeprazole on the coagulation time and plasma warfarin concentration was measured in patients receiving continuous therapy with warfarin. Plasma S-warfarin concentrations were not significantly affected by the co-administration of omeprazole in these patients and there was no significant change in the coagulation time. The results presented recently by...

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### Table 2. World-wide vitamin K antagonist interactions (with bleeding event or blood abnormality)

<table>
<thead>
<tr>
<th>PPI</th>
<th>Drug packages supplied world-wide (millions)</th>
<th>Interactions with PPI as PS or SS</th>
<th>Frequency per package</th>
<th>Interactions with PPI as PS or sole co-medication</th>
<th>Frequency per package</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>950.1*</td>
<td>81</td>
<td>0.09 per million</td>
<td>20</td>
<td>0.02 per million</td>
</tr>
<tr>
<td></td>
<td>13.1†</td>
<td>1</td>
<td>0.08 per million</td>
<td>1</td>
<td>0.08 per million</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>195.4‡</td>
<td>21</td>
<td>0.11 per million</td>
<td>5</td>
<td>0.03 per million</td>
</tr>
<tr>
<td></td>
<td>22.1§</td>
<td>5</td>
<td>0.23 per million</td>
<td>3</td>
<td>0.14 per million</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>79.6¶</td>
<td>9</td>
<td>0.11 per million</td>
<td>6</td>
<td>0.08 per million</td>
</tr>
</tbody>
</table>

PPI, proton pump inhibitor; PS, primary suspect; SS, secondary suspect.

* October 1989 to September 2001 (i.e. from US launch).
† October 1989 to April 1991 (i.e. first 19 months after US launch).
‡ June 1995 to September 2001 (i.e. from US launch).
§ June 1995 to December 1996 (i.e. first 19 months after US launch).
¶ February 2000 to September 2001 (i.e. first 19 months after US launch).
McCarthy et al. suggest that gastrointestinal bleeding events in elderly patients are more common in patients taking omeprazole or lansoprazole together with warfarin than in patients taking warfarin alone. The conclusions drawn from these results need to be viewed with caution, however, as the authors may have confused causality with association. For example, it was also observed in the same study that patients taking omeprazole or lansoprazole together with non-steroidal anti-inflammatory drugs (NSAIDs) had more gastrointestinal bleeding events than patients taking NSAIDs alone, with the conclusion that these proton pump inhibitors were in some way responsible for the bleeding events. This seems unlikely, as it has been shown, at least for omeprazole, that it does not change the bioavailability of the NSAIDs diclofenac, naproxen and piroxicam. It seems more likely that omeprazole or lansoprazole was given to these patients because of their bleeding problems during NSAID treatment.

The interaction effects of pantoprazole with vitamin K antagonist drugs have been studied for single-dose warfarin and for phenprocoumon in healthy volunteers. In both studies, plasma levels of the drugs remained within the range of bio-equivalence. To our knowledge, no studies have been performed in patients on warfarin therapy, with the exception of a recent study which showed a statistically significant but very small decrease in anticoagulant control in patients receiving various proton pump inhibitors, including pantoprazole, together with warfarin. The authors suggested that the results may have been confounded by the increased age and lower testing frequency in the proton pump inhibitor group compared with controls, making the results inconclusive.

Adverse events resulting from suspected vitamin K antagonist interactions were rare for all three proton pump inhibitors in our search, contradicting previous suggestions that pantoprazole is safer than omeprazole and lansoprazole because it has a lower potential for interaction. The results do, however, confirm our view, and that of others, that there is no major clinical problem relating to the co-administration of vitamin K antagonists with proton pump inhibitors. The frequency of adverse events resulting from suspected interactions was found to be very small, and sufficiently similar for all three proton pump inhibitors to suggest that the interaction was either a class effect (rather than being specific to one proton pump inhibitor), or a random coincidence.

It seems probable that only an isolated sub-group of predisposed individuals may be at risk from proton pump inhibitor–vitamin K antagonist interactions and may require adjustment of their anticoagulant dose. Predispositions could arise from deficiencies in the isoforms of cytochrome P450 (CYP) that predominantly account for the metabolism of the drugs concerned: CYP2C19 for proton pump inhibitors and CYP2C9 for warfarin. Owing to genetic polymorphism, some individuals will show reduced or absent expression of the respective isoforms, and may be classified as ‘slow metabolizers’. As a result, warfarin may compete for other enzyme breakdown pathways, such as CYP3A4, which participates in the bio-transformation of omeprazole, lansoprazole and pantoprazole, and is able to contribute to S-warfarin hydroxylation. On the other hand, proton pump inhibitors may inhibit or compete for CYP2C9, the predominant isoform involved in S-warfarin metabolism. As the affinity of the proton pump inhibitors for 2C9 is not high, such interactions are highly unlikely to occur in normal metabolizers, but may prevail at high plasma concentrations. The recently reported interaction of pantoprazole with methotrexate suggests that pantoprazole metabolites may also compete with other drugs for renal elimination. This needs further study.

The main conclusion of our study is that interactions of proton pump inhibitors with other drugs, including vitamin K antagonists, are rare and do not constitute a major clinical risk. The finding that pantoprazole was associated with at least as many vitamin K antagonist interactions as omeprazole and lansoprazole, per drug package, suggests that these represent a ‘class effect’ and negates claims that pantoprazole has fewer interactions than other proton pump inhibitors. It can no longer be considered to be a safer proton pump inhibitor on the basis of inference from results obtained in small numbers of healthy volunteers.

ACKNOWLEDGEMENT

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