Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database

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Abstract

Objectives: To establish the relation between new prescriptions for proton pump inhibitors and recorded upper gastrointestinal morbidity within a large computerised general practitioner database.
Design: Retrospective survey of morbidity and prescribing data linked to new prescriptions for proton pump inhibitors and comparison with licensed indications between 1991 and 1995.
Setting: General Practice Research Database and prescribing analysis and cost (PACT) data for the former West Midlands region.
Subjects: Information for 612 700 patients in the General Practice Research Database. Anonymous PACT data for all general practitioners in West Midlands region.
Main outcome measures: Diagnostic codes linked to the first prescriptions issued for proton pump inhibitors; relation between new prescriptions and licensed indications; yearly change in ratio of new to repeat prescriptions and prescribing volumes measured as defined daily doses.
Results: Oesophagitis was the commonest recorded indication in 1991, accounting for 31% of new prescriptions, but was third in 1995 (14%). During the study new prescriptions increased substantially, especially for duodenal disease (780%) and non-ulcer dyspepsia (690%). In 1995 non-specific morbidity accounted for 46% of new prescriptions. The total volume of prescribing rose 10-fold between 1991 and 1995, when repeat prescribing accounted for 77% of the total.
Conclusions: Changes in recorded morbidity associated with new prescriptions of proton pump inhibitors did not necessarily reflect changes in licensed indications. Although general practitioners seemed to respond to changes in licensing, particularly for duodenal and gastric disease, prescribing for unlicensed indications non-ulcer dyspepsia and non-specific abdominal pain increased.

Introduction

Dyspeptic symptoms are a common presenting complaint to general practitioners, and there is continuing debate about management.[1] Acid suppressant drugs, the most potent of which are proton pump inhibitors, are often prescribed, and it has been suggested that proton pump inhibitors are "probably too widely prescribed for minor symptoms, and the cost implications of this are clear."[2] The first proton pump inhibitor, omeprazole, was introduced in 1989, since when two further drugs in the class have been marketed, lansoprazole and pantoprazole. There has been a substantial, continuing, and unexplained rise in prescribing of proton pump inhibitors, which now account for over 6% (£23m) of primary care expenditure on drugs in the West Midlands region. It is unknown whether their use in practice has corresponded to their licensed indications.

General practitioners, health authorities, and their advisers use prescribing analysis and cost (PACT) data to monitor prescribing in primary care and interpret trends. A recognised disadvantage of PACT data is the inability to link prescribing directly with morbidity or individual patients.[3,4] The General Practitioner Research Database, previously known as VAMP Research, is a UK database recording morbidity, prescribing data, and referrals and provides a resource for monitoring drug use and appropriate prescribing.[5–7] Anonymised records of individual patients are allocated a unique patient number. Data on medical events, patient problems, and other doctor-patient interventions are captured in the database by means of codes from the Oxford Medical Information System (OXMIS) dictionary. The dictionary was based initially on an amalgamation of the eighth revision of the *International Classification of Diseases* (ICD-8) and surgical operation codes of the Office for National Statistics. General practitioners who provide data have agreed to record information in a standard manner, which can be used for research purposes. The General Practitioner Research Database for the former West Midlands region contains 33 million records for prescribing or diagnosis for a population of 612 700 patients. The age-sex profile of the patients matches that for the West Midlands region and England and Wales.[8]

Using the General Practitioner Research Database for the years 1991-5, we identified new prescriptions for proton pump inhibitors and analysed the associated clinical data, comparing the results with the

Table 1 Dates of licensed indications for omeprazole and lansoprazole

	Omeprazole	Lansoprazole
June 1989	Short term treatment of peptic ulceration	
September 1989	Treatment of reflux oesophagitis	
February 1990	Prophylaxis for NSAID induced ulceration	
November 1991	Long term treatment of reflux oesophagitis	
January 1993	Treatment of oesophageal reflux	
January 1994	Long term treatment of duodenal ulcer	
April 1994	Treatment of *Helicobacter pylori* infection (dual therapy)	
May 1994		Treatment of duodenal ulceration, benign gastric ulceration, and gastro-oesophageal reflux
January 1995	Prophylaxis of acid aspiration	
January 1996	Eradication of *H pylori* (7 day triple therapy)	Long term treatment of peptic ulceration
February 1996		Eradication of *H pylori*
January 1997		Treatment of dyspepsia
April 1997	Treatment of non-ulcer dyspepsia	
December 1997		Treatment of Zollinger-Ellison syndrome

NSAID=non-steroidal anti-inflammatory drug.

licensed indications. The licensed indications for lansoprazole, introduced in 1994, were more restricted than those for omeprazole (table 1). Pantoprazole, available since 1996, falls outside the years that we investigated. To establish whether the results could be applied to the interpretation of PACT data for proton pump inhibitors, we determined that the prescribing trends for the General Practitioner Research Database and PACT data matched.

Methods

We extracted all records of prescribing of a proton pump inhibitor within the General Practitioner Research Database and analysed them using Microsoft Access software. For individual patient records, two of us (a general practitioner and a medical adviser) reviewed OXMIS diagnosis codes that were linked to prescribing of proton pump inhibitors. We grouped 205 codes that could be reasonably linked to gastrointestinal disease or presenting complaints into eight categories (table 2). A consultant gastroenterologist verified this categorisation, which is available on request.

All records for patients who had been prescribed a proton pump inhibitor were divided into calendar years from 1991 to 1995. From 1991, we identified the first prescription of a proton pump inhibitor for each patient and extracted the record with the OXMIS code and data to calculate defined daily doses. Subsequent years' data were similarly analysed, and patients from preceding years excluded, thus separating patients newly prescribed proton pump inhibitors from those given repeat or recurrent prescriptions. Patients with a relevant OXMIS code were then placed into one of the eight categories.

Table 2 Number of morbidity codes from OXMIS* per category of gastrointestinal disease

Disease category	No of codes
Duodenal	15
Gastric	25
Ulcer unspecified	10
Oesophagitis	11
Hiatus hernia and reflux	8
Non-ulcer dyspepsia	16
Non-specific abdominal pain	4
Miscellaneous upper gastrointestinal	118

*Oxford Medical Information System.

Two of us reviewed the relevant data fields and developed an algorithm to convert the data on the drug's quantity, strength, and duration into defined daily doses. The defined daily dose is the assumed average dose per day for a drug used for its main indication in adults, as defined by the World Health Organisation, and is an internationally recognised comparator for research into drug use.[9] Thirty three records (0.05%) lacked the necessary data for conversion to defined daily doses and were discarded with negligible effect on the final calculation. We analysed quarterly PACT data from June 1991 to December 1995 for proton pump inhibitors for the former West Midlands region and similarly converted these to defined daily doses.

Statistical analysis

For both sets of data, we plotted the trend over time and performed regression analyses to test the linearity of the trends. We used Wilcoxon's matched pairs signed ranks test to compare the rate of change in defined daily doses between two consecutive quarters for both trends, and to test for a difference in the median rate of changes between the two sets. Finally, for each year, we calculated the defined daily doses for first prescriptions for all new patients and subtracted these from the total to quantify repeat prescribing.

Results

Table 3 shows the numbers of new prescriptions of proton pump inhibitors and their clinical indications. During the study period the largest absolute increases in recorded clinical indications for starting proton pump inhibitors were duodenal disease (780%), non-ulcer dyspepsia (690%), gastric disease (450%), and non-specific abdominal pain (390%). The smallest increase was for oesophagitis (75%).

There were significant changes in prescribing for different disease categories over time. In 1991 oesophagitis was the largest category (31% of the total), but in 1995 it was only the third largest (14%) after non-ulcer dyspepsia (32%) and hiatus hernia and reflux (17%). Prescribing for duodenal disease increased at the time omeprazole was licensed for long term treatment of

Table 3 Numbers (percentages) of new prescriptions of proton pump inhibitors and their clinical indications

Clinical indication	Year of study				
	1991 (n=731)	1992 (n=1400)	1993 (n=1847)	1994 (n=2573)	1995 (n=2908)
Licensed indications					
Duodenal disease	42 (5.7)	86 (6.1)	124 (6.7)	264 (10.3)	369 (12.7)
Gastric disease	41 (5.6)	71 (5.1)	121 (6.6)	191 (7.4)	224 (7.7)
Ulcer unspecified	18 (2.5)	39 (2.8)	30 (1.6)	73 (2.8)	66 (2.3)
Oesophagitis	226 (31)	287 (20.5)	399 (21.6)	433 (16.9)	396 (13.6)
Hiatus hernia and reflux	—	—	400 (21.6)	455 (17.7)	507 (17.4)
Subtotal	327 (44.8)	483 (34.5)	1074 (58.1)	1416 (55.1)	1562 (53.7)
Unlicensed indications					
Hiatus hernia and reflux	171 (23.4)	351 (25.1)	—	—	—
Non-ulcer dyspepsia	116 (15.9)	314 (22.4)	459 (24.9)	664 (25.8)	918 (31.6)
Non-specific abdominal pain	29 (3.9)	73 (5.2)	67 (3.6)	119 (4.6)	141 (4.8)
Miscellaneous gastrointestinal disease	88 (12.0)	179 (12.8)	247 (13.4)	374 (14.5)	287 (9.9)
Subtotal	404 (55.2)	917 (65.5)	773 (41.9)	1157 (44.9)	1346 (46.3)

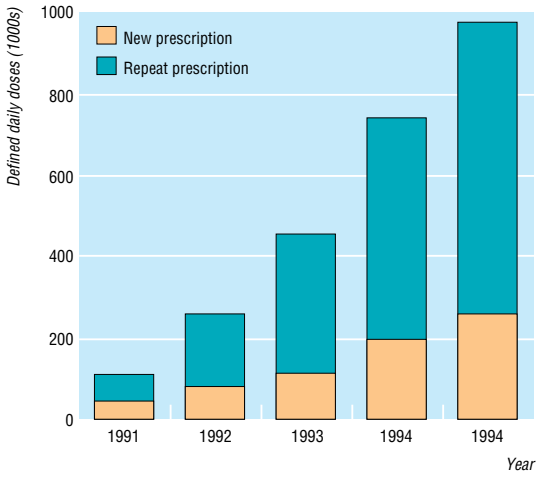

Fig 1 Proportions of new and repeat prescriptions for proton pump inhibitors during 1991-5 (data from General Practitioner Research Database)

this condition, whereas prescribing for non-ulcer dyspepsia increased steadily throughout the study period despite the drugs not being licensed for this condition until April 1997. Most of the data relate to omeprazole: the proportion of defined daily doses accounted for by lansoprazole was 2.5% in 1994, rising to 6.4% in 1995 (table 4).

During the study, the total volume of prescribing increased 10-fold. The percentage contribution from new prescriptions decreased yearly from 29% in 1992 to 23% in 1995 (fig 1). The proportion attributable to repeat prescribing (77%) accords with previous work, which established that repeat prescriptions generally account for 75% of the volume and 81% of the cost of prescribing.[10]

Figure 2 shows that the prescribing of proton pump inhibitors, as measured by defined daily doses, increased linearly for both the data from the General Practitioner Research Database and from PACT (regression analysis slope = 2727.3 for PACT data, 157.4 for General Practitioner Research Database). Both data sets had the same coefficient of determination (98.5%), indicating a high degree of fit. The P value (0.913) for Wilcoxon's matched pairs signed ranks test ($z = -0.109$) was not significant at the 1% level of significance, indicating that the two data sets had the same rate of change. The median (interquartile range) values were 0.524 (0.471-0.566) for PACT and 0.521 (0.356-0.632) for the General Practitioner Research Database, indicating that the rates of change also had the same distribution.

Table 4 Relative contributions of omeprazole and lansoprazole to total prescriptions of proton pump inhibitors

	No (%) of defined daily doses	
	1994	1995
Omeprazole	11 931 813 (97.5)	16 134 917 (93.6)
Lansoprazole	311 225 (2.5)	1 099 981 (6.4)
Total	12 243 038	17 234 898

Discussion

The purpose of this study was to examine the clinical reasons recorded by general practitioners when prescribing proton pump inhibitors to patients for the first time. Diversity of diagnostic labelling between doctors is inevitable, and we are aware that the recorded indication could, as Marinker stated, be "not so much the basis for the choice of drug but rather the alibi for it."[11] Also, the diagnosis could change from that initially entered. Despite these limitations, the coding entered when a patient is first prescribed a proton

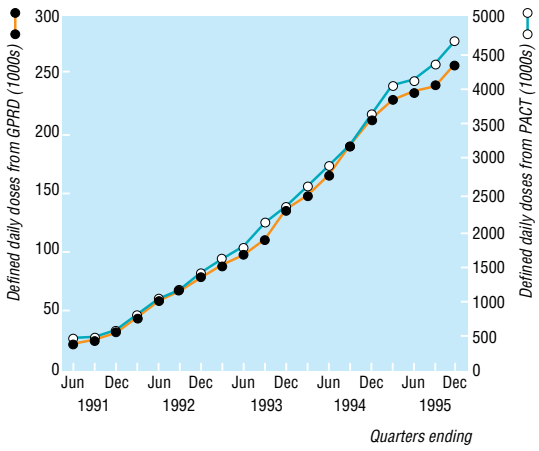

Fig 2 Total prescriptions for proton pump inhibitors during 1991-5 according to General Practitioner Research Database (GPRD) and prescribing analysis and cost (PACT) data

pump inhibitor is deemed to reflect the perceived clinical reason at that time.

Prescribing patterns

The first licensed indication for which proton pump inhibitors represented a major advance in treatment was reflux oesophagitis, so this might reasonably be expected to be a major driver in the increase in new prescribing. This was not the case: the proportion of new prescriptions for this condition fell steadily between 1991 and 1995 and accounted for only 8% of the total increase in new prescriptions. This decrease is explained in part by the expansion of the licensed indications, with appropriate increases in new prescribing for duodenal and gastric disease.

However, throughout the study a substantial amount of prescribing was linked to unlicensed indications. This varied from 65% in 1992 to 41% in 1993, when licensed indications were expanded. During 1991 and 1992 hiatus hernia and reflux disease was the largest contributor, but on revision of licensing this was replaced by non-ulcer dyspepsia. Throughout the study, the proportion of new prescribing for non-ulcer dyspepsia increased from 16% to 32%, despite the drugs not being licensed for this indication until 1997. A further 15% of patients newly prescribed proton pump inhibitors were categorised as having non-specific abdominal pain or miscellaneous upper gastrointestinal disease. If this ratio of new prescriptions is carried over into repeat prescriptions nearly a half of the current national annual expenditure of £247m could be for non-specific upper gastrointestinal symptoms.

Limitations of study

We may have underestimated unlicensed use of proton pump inhibitors for several reasons. In some categories such as duodenal disease there is a mixture of codes reflecting licensed and unlicensed indications, but the category as a whole was designated as licensed. The inclusion of lansoprazole, which at the time of introduction had more restrictive licensing than omeprazole, will also have underestimated the proportion of new prescriptions for unlicensed indications.

Missing diagnostic data (range per year 19.3%-28.3%) was another potential bias, but this was expected. For data gathering exercises, such as surveys, a response rate of 70% is considered acceptable.[12] Jick et al found that 87% of diagnostic information from consultant letters was present on the VAMP computer systems in one study, and in a repeat study with a different group of practices the proportion was 96%.[5 6] Nazareth et al noted the recording of psychotic illness on VAMP to be "accurate and complete."[13] However, consultant opinion or confirmation by investigation is more likely to result in the recording of a definitive diagnosis such as duodenal ulcer or oesophagitis, whereas this applies in only a minority of cases of gastrointestinal illness in primary care. It is possible, therefore, that unconfirmed diagnoses are less likely to be entered, resulting in an underestimate for categories such as non-specific abdominal pain, non-ulcer dyspepsia, and, possibly, hiatus hernia and reflux. It has been postulated that general practitioners who maintain computerised records to research standards differ from most of their colleagues.[14]

Key messages

- There has been much speculation about the reasons behind the substantial rise in prescribing of proton pump inhibitors, especially their use for minor symptoms.
- We used the General Practitioner Research Database for the former West Midlands region to show that the volume of proton pump inhibitor prescribing rose 10-fold between 1992 and 1995 and repeat prescribing had risen to 77% of the volume by 1995
- Prescribing for uncomplicated dyspepsia and non-specific abdominal symptoms, which were outside the licensed indications, accounted for 46% of new prescribing by 1995
- The proportion of prescribing for the licensed indication of oesophagitis fell during the study, but that for duodenal ulceration increased in line with the expansion of licensed indications
- Analysis of PACT data showed similar prescribing trends to those found with the General Practitioner Research Database

Implications of study

We have demonstrated that the General Practitioner Research Database and PACT show similar trends for prescribing of proton pump inhibitors and that the proportion of repeat prescribing is close to that reported in other studies. We infer that both the subset of West Midland general practitioners providing data for the General Practitioner Research Database and general practitioners throughout the region have responded in a similar manner to the influences that have produced this change in prescribing. It is therefore reasonable to assume that the number of different diagnoses contributing to this rise is similar for both the General Practitioner Research Database and PACT populations.

Reasons for prescribing outside licensed indications are manifold. Influences as diverse as recommendations from hospital colleagues, drug companies' marketing, and patient pressure have all been shown to have an effect, although there is some evidence that patient pressure is less important than general practitioners perceive.[15–20] Concerns about the long term safety of proton pump inhibitors and their overuse for minor symptoms have been expressed,[2] but only recently have authoritative guidelines been published that may help general practitioners to prescribe proton pump inhibitors more appropriately.[21 22] Although many doctors remain resistant to guidelines, greater willingness to accept their recommendations and more emphasis on implementing them should constrain the future use of proton pump inhibitors.

Conclusions

In 1991, 54% of patients newly prescribed proton pump inhibitors were recorded as having gastro-

oesophageal reflux disease, followed by 32% with non-specific indications, and 14% with "ulcer" disease. These proportions had changed in 1995 to 31%, 46%, and 23% respectively, and do not necessarily reflect changes in licensed indications. Although general practitioners seemed to have responded to changes in licensing, particularly for duodenal and gastric disease, we found there had also been increasing use of proton pump inhibitors for non-ulcer dyspepsia and non-specific abdominal pain.

The General Practitioner Research Database enabled us to achieve a better understanding of prescribing activity than was possible with routine prescribing data, and this may be relevant to other therapeutic areas.

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Letter from South Africa

Tree bug

There are two common conditions that affect doctors who work at Mosvold Hospital. One is tick bite fever. Almost every new doctor is confidently diagnosed as a sufferer sooner or later. We do not have the serology for confirmation. It is, however, of note how often it is diagnosed among medical staff and how rarely in patients. Most patients have to make do with less distinguished illnesses such as flu and perhaps an infected insect bite. There are a lot of ticks around. There are also a lot of mosquitoes; not to mention the 80 000 described insect species and 3000 species of spider and the thousands of undescribed bugs of various kinds, many of which are not averse to giving you a nasty nip if they have the chance. Colds are also common, although less often diagnosed among medical staff.

The other affliction that seems to affect a substantial number of staff, particularly if they remain exposed to the bush long enough, is tree bug. I admit to being a sufferer of this condition. It starts by wondering about the strange palm tree outside your house. Eventually you discover that it is a cycad, a plant that is more or less the same as when the dinosaurs were around. You ask a Zulu what the tree with dazzling red flowers against the dry August bush is, and are disappointed by the lack of an answer. After a while you learn that it is a coral tree. Then you wonder why some large local trees seem so oddly twisted, and it turns out that they are strangler figs; and so it goes on.

South Africa has 16 times as many tree species as the whole of northern Europe. The garden of a previously tree bugged doctor has a fine botanical collection and his efforts have many patients sitting under them on a hot day. A teacher in Ingwavuma has tree bug so badly that when he goes to a game park he can hardly see the rhinos, so absorbed is he by what they are eating. Then come some less pleasant discoveries. Australian gum trees have been stuck all over southern Africa, not only in vast plantations but apparently as some marker of civilisation in a really quite bizarrely unimaginative way. You learn that South Africa has less than 1% of its original forest remaining. It seems that disrespect for African people was paralleled with disrespect for African vegetation. One exception is the baobab tree. On the drive north to Zimbabwe it seems that whereas all the other plants made way for the road, the road has been routed around the huge baobabs.

The tide against indigenous plants does now seem to be turning, although it will take time to reverse decades of ruthless exotic planting. Richard's Bay and Durban now have an indigenous tree policy. Newly planted saplings are usually mahoganies, fever trees, giant leafed figs, wild bananas, or wild date palms, rather than the jacarandas and flamboyants. Once there were few books to be found on the subject, whereas now there is quite a choice.

CH Vaughan Williams, *principal medical officer, Ingwavuma, South Africa*

We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to.