ORIGINAL ARTICLE

Dosing of proton pump inhibitors in a private hospital in Hong Kong

CME

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Objective To study the prescribing pattern of proton pump inhibitors with regard to the time of dosing.

Design Retrospective study.

Setting Private hospital, Hong Kong.

Patients All patients prescribed three specific proton pump inhibitors from 1 January to 31 July 2006 were included.

Main outcome measures For all three proton pump inhibitors, the prescribed dosing instructions were recorded as well as the specialties of the corresponding prescribers.

Results The ratio of doctors prescribing proton pump inhibitors before meals versus at other times was 1:105. The ratio of patients receiving proton pump inhibitors before meals versus at other times was 1:341. The number of tablets of proton pump inhibitors prescribed before meals versus at other times was 1:409.

Conclusions The overwhelming majority of doctors in this study did not prescribe proton pump inhibitors before meals.

Introduction

Proton pump inhibitors (PPIs) are benzimdazoles, which as a group aim at inhibiting gastric acid secretion. Five different PPIs were available in Hong Kong when this audit was carried out. Apart from the brand name products, one of them (omeprazole) was also available as a generic form. Whilst PPIs are widely used in medical practice for various indications, in recent years there is an increasing trend towards long-term usage.[1-3] Long-term indications include gastric protection for patients taking non-steroidal anti-inflammatory drugs (NSAIDs) regularly (including aspirin), maintenance therapy for gastro-oesophageal reflux diseases (GERD), and for non-cardiac chest pain.

All PPIs exert their anti-secretary effect only on parietal cells with activated proton pumps. Proton pumps are mainly activated by food. Hatlebakk et al[4] reported that when omeprazole or lansoprazole was given with breakfast, the median percentage of time during which the gastric pH was <4.0 was 17.2%, compared to 42.0% when taken without food. There is a sound pharmacological basis (see below) and ample clinical evidence indicating that to achieve optimal acid suppression, PPIs should be used before meals. Gunaratnam et al[5] reported that sub-optimal PPI dosing (defined as dosing >1 hour before meals, after meals, at night time, or when needed) was common in patients with poorly controlled GERD, the estimated prevalence being 54%.[5]

Despite these publications, sub-optimal use of PPIs is prevalent among the medical professionals in western countries.[6] To the best of our knowledge, there have been no studies and no corresponding data available on PPI-prescribing habits of the local medical profession. Therefore the objective of this study was to audit doctors' prescribing patterns with regard to PPI dosing in a private hospital setting in Hong Kong. Specifically, we aimed to find the proportion of PPIs prescribed before meals (AC), after meals (PC), at night (Nocte), as needed (PRN) or without dosing advice other than the number of times to take a dose each day, ie non-specified (NS).

Pharmacokinetics

Proton pump inhibitors are pro-drugs. All oral PPI formulations are protected from gastric acidity, to enable their absorption in the small intestine. After absorption, on reaching gastric parietal cells, they are protonated (activated) to exert their action. The plasma

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elimination half-life is usually 2 hours or less.[7] Among PPIs, absorption is variably affected by food. Accordingly, the manufacturers of PPIs have varied dosing instructions based on pharmacokinetics (PK) considerations, as outlined below:

(1) Pantoprazole (Pantoloc; Altana, Oranienburg, Germany) absorption "*may be delayed by 2 hours if taken with food*". The manufacturer stresses AC dosing and advises it should be "*swallowed …one hour before breakfast…the second Pantoloc should be taken before the evening meal*" (product insert).

(2) Lansoprazole (Takepron; Takeda, Osaka, Japan) bioavailability is "*reduced by about 50% if taken immediately after meal. If breakfast is taken 30 minutes after the dose of lansoprazole, there are no significant differences in Cmax and AUC*". Accordingly, the manufacturer of Takepron advises that it should be taken "*fasting, and a meal should be taken at least 30 minutes later*" (personal communication).

These two PPI brands, namely pantoprazole and lansoprazole, are therefore by default pre-labelled "to be taken before meals" by our Hospital Pharmacy and corresponding advice is offered to patients. For the same reason, they were excluded from the present study.

(3) Rabeprazole (Pariet; Eisai, Tokyo, Japan) manufacturer states that "*neither the time of the day nor food intake was shown to have any effect on rabeprazole sodium activity*". Its advice on AC dosing ("*taken in the morning, before eating*") is only intended "*to facilitate treatment compliance*" (product insert).

(4) Omeprazole (Losec; AstraZeneca, Södertälje, Sweden) manufacturer states that "*concomitant food intake has no influence on the bioavailability*" (product insert), and does not advise on its AC dosing.

(5) Esomeprazole (Nexium; AstraZeneca, Södertälje, Sweden) prescribing instruction states that "*food intake both delays and decreases the absorption of esomeprazole*" but "*this has no significant influence on the effect of esomeprazole on intragastric acidity*" and likewise does not advise on AC dosing in its product insert.

The Hospital Pharmacy has by default not labelled AC dosing for rabeprazole, omeprazole, and esomeprazole. Dosing advice for these three PPIs depends on instructions from prescribing doctors, and their prescribing was therefore audited in this study.

Pharmacodynamics

Gastric acid secretion is mediated by the enzyme H^+/K^+ ATPase, also known as the proton pump (PP), in gastric parietal cells. The PP is manufactured in the endoplasmic reticulum and stored in the Golgi apparatus, and after a meal, about 70 to 80% is activated. When the parietal cell is stimulated by food, the PP is carried to the membrane of the canaliculi, where it exerts its action of acid secretion. Proton pump inhibitors are activated in the acidic environment of the secretary canaliculi of parietal cells, where they covalently inhibit the PP, thus inhibiting acid secretion. Only about 5% of the PP is active in the fasting state, 95% being inactive, in which case PPIs are virtually ineffective. Thus, to facilitate maximal gastric acid suppression by PPIs, they should be taken prior to food, so that they reach the parietal cells when the PP becomes active.[4,7]

香港一所私家醫院的質子泵抑制劑施用情況

目的 從施用的時間，細察施用質子泵抑制劑的模式。

設計 回顧研究。

安排 香港一所私家醫院。

患者 2006年1月1日至7月31日期間，所有由醫生處方使用三次個別質子泵抑制劑的病患者。

主要結果測量 三次質子泵抑制劑的醫生處方用藥指示，以及負責處方的醫生。

結果 醫生處方在餐前服用質子泵抑制劑相對於其他時間服用的比率為1:105，病患者在餐前服用質子泵抑制劑相對於其他時間服用的比率為1:341，而醫生處方要在餐前服用質子泵抑制劑藥片的數量相對於其他時間的用藥數量比率為1:409。

結論 本研究顯示，絕大部分醫生不會處方在餐前施用質子泵抑制劑。

Methods

This study was performed in a private hospital in Hong Kong (Hong Kong Baptist Hospital) providing both general practice and specialist care. It targeted all PPIs prescribed during the study period, which were not by default pre-labelled to be taken before meals (as was the case for lansoprazole and pantoprazole). Thus, this audit was confined to the prescribing of omeprazole, esomeprazole, and rabeprazole. Prescriptions for these PPIs with incomplete data (name, specialty, etc) were classified as 'invalid' and were also excluded.

Prescribing of the three targeted PPIs in the hospital from 1 January to 31 July 2006 was audited. Data collected included: the amount of each drug used, the amount of each prescribed AC, PC, Nocte, or NS, the numbers of patients receiving AC versus non-AC dosing, the numbers of doctors prescribing each category, and their respective specialties.

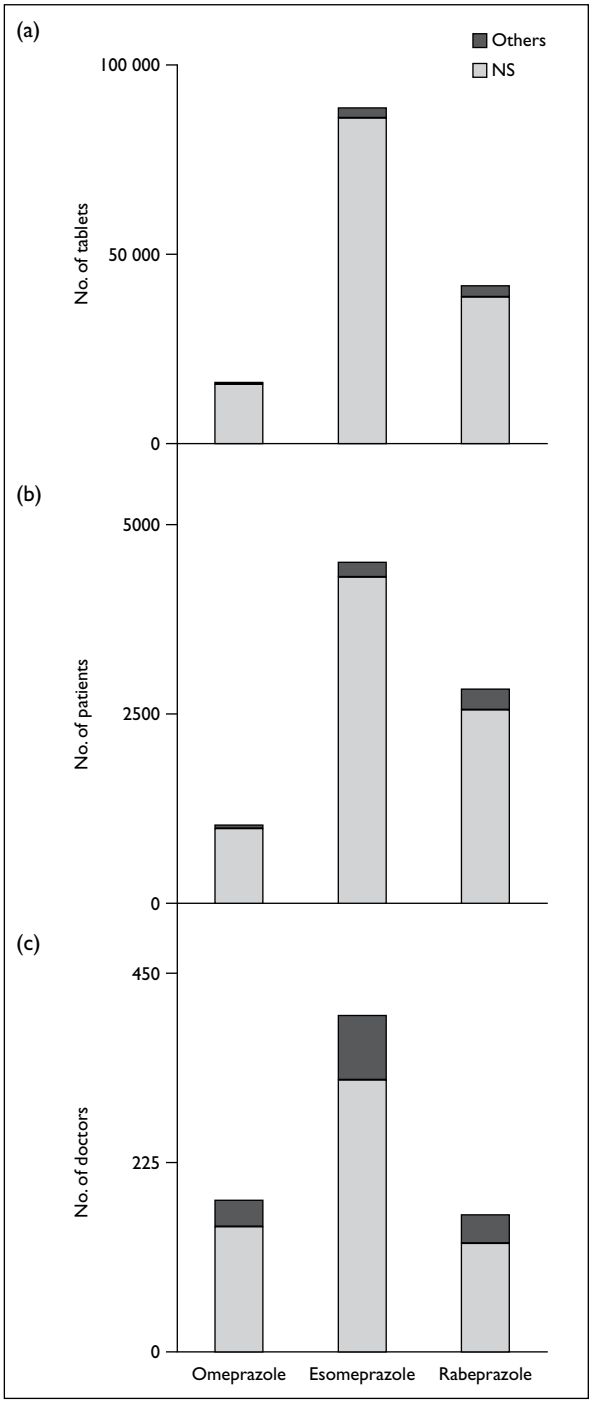

FIG 1. (a) Proton pump inhibitors (PPI) usage from 1 January to 31 July 2006, showing (a) number of tablets prescribed, (b) number of patients taking PPI, and (c) number of doctors prescribing PPI

NS denotes dosing time not specified, and others include taking before and after meal, at night, and when needed

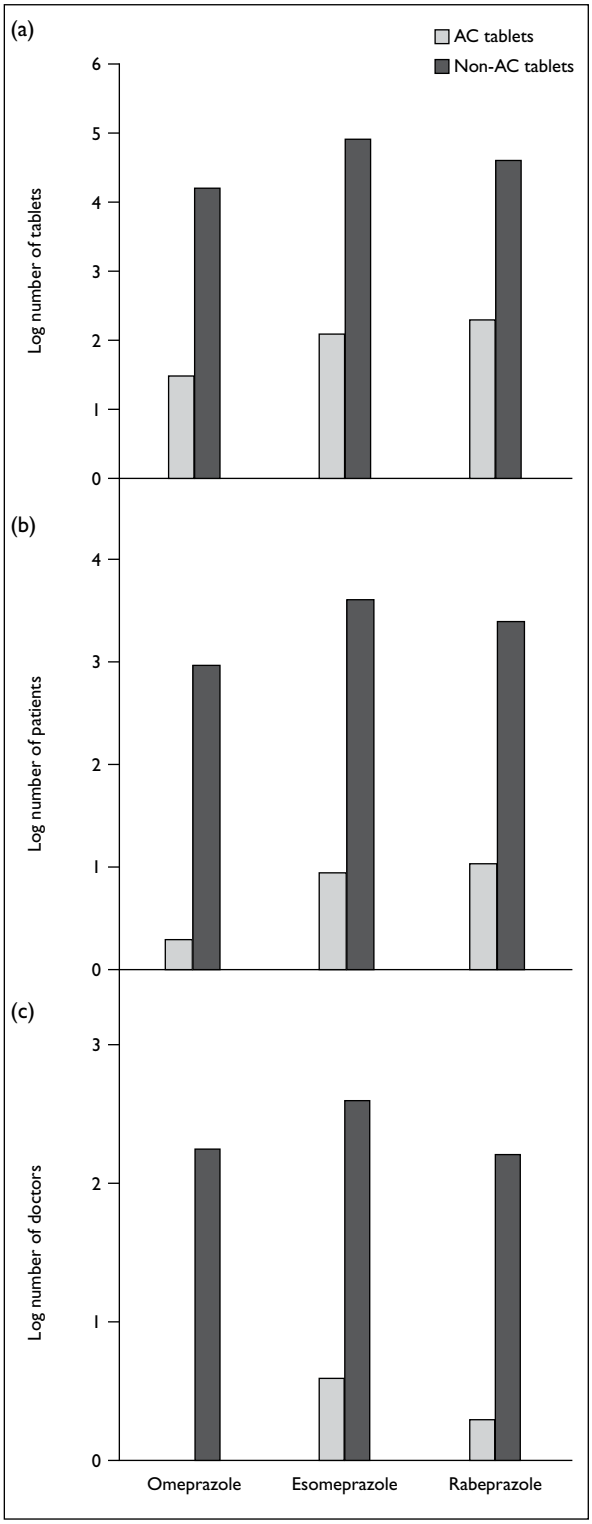

FIG 2. Log numbers of (a) tablets prescribed AC (before meal) versus non-AC, (b) patients receiving AC (before meal) dosing versus non-AC dosing, and (c) doctors prescribing AC (before meal) dosing versus non-AC dosing

Results

The gross data retrieved are shown in Figure 1. Of the three PPIs studied (omeprazole, esomeprazole, and rabeprazole), 148 100 tablets were prescribed during this 7-month period. Of these, prescriptions for 1300 (0.9%) tablets were invalid (due to incomplete data) and excluded from the analysis. Of the remaining 146 800 tablets, esomeprazole usage comprised 61%, rabeprazole 28%, and omeprazole 11%. The two PPIs

(lansoprazole and pantoprazole) excluded from the audit amounted to 75 800 tablets. In the following analysis, AC dosing was compared to all other dosing regimens (PC, Nocte, PRN, and NS) grouped together as non-AC dosing.

Tablet, patient, and prescriber analysis

For the audited PPIs, the numbers of tablets prescribed AC (AC tablets) and non-AC (non-AC tablets) are shown in Figure 2a. In numerical terms, the ratio of all AC versus non-AC tablets prescribed is 1:409. The pre-dominance of non-AC tablet prescribing held true for all the PPIs. The patient numbers taking the audited PPIs AC (AC patients) and non-AC (non-AC patients) are represented in Figure 2b. The overall ratio of patients receiving AC dosing versus non-AC dosing was 1:341. The predominance of patients receiving non-AC dosing was evident for all PPIs studied. The numbers of doctors prescribing the audited PPIs AC (AC doctors) and non-AC (non-AC doctors) are shown in Figure 2c. The overall ratio of AC versus non-AC doctors was 1:105, and the same trend was observed across all PPIs.

Among the non-AC tablets prescribed, the overwhelming majority (>85%) were in the NS category (Fig 3).

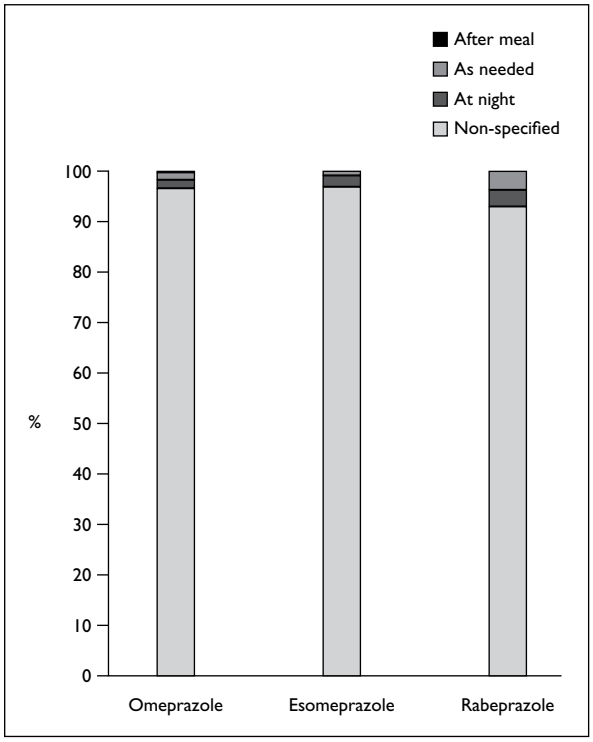

FIG 3. Analysis of non-AC dosing

Prescribing according to specialist categories

The relative number of AC and non-AC prescribers among gastroenterologists is shown in Figure 4. With the exception of a small minority of gastroenterologists, virtually all prescribers in all specialties did not specify AC dosing when prescribing the audited PPIs. The overall ratio of AC to non-AC prescribers even among gastroenterologists was 1:5.6. Thus, less than 20% of relevant specialists actually specified AC dosing.

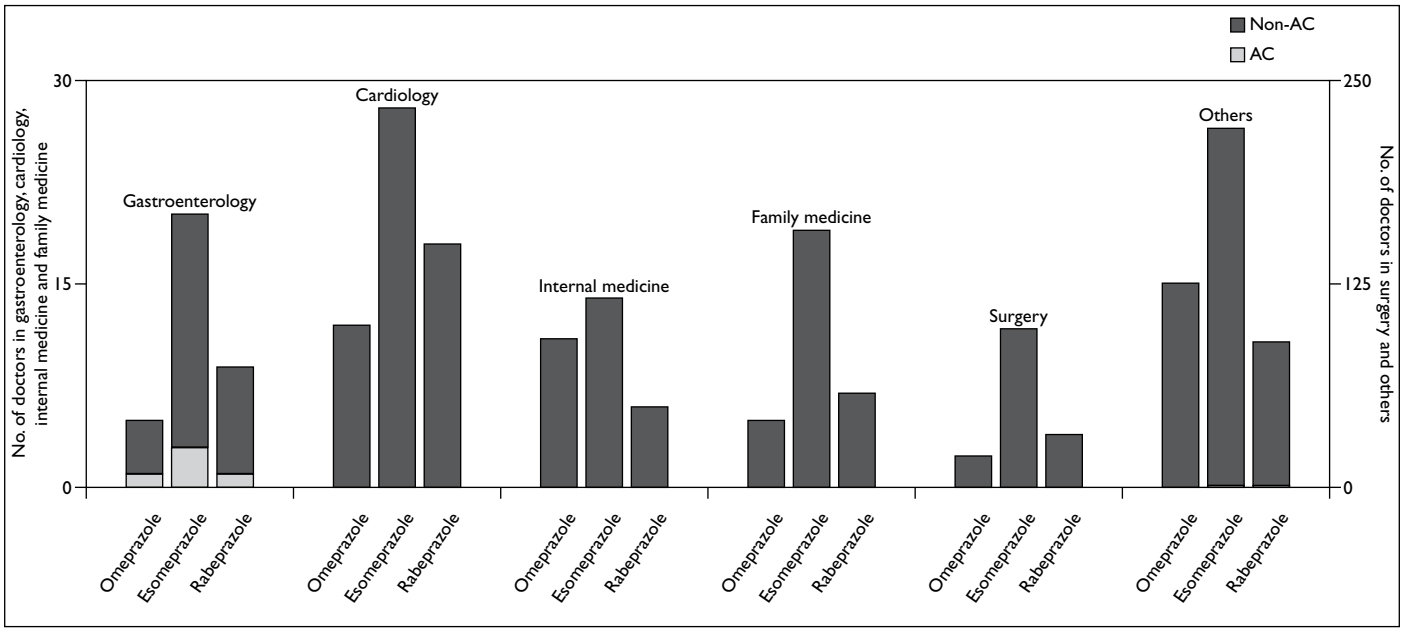

FIG 4. Number of doctors by specialty

Discussion

From the above audit, it is apparent that most doctors, including gastroenterologists, were not specifying AC dosing for the audited PPIs and therefore most patients were very likely not taking them before meals. For patients with GERD, the aim of treatment is to maintain intra-gastric pH above 4 for at least 12 to 16 hours during the 24-hour period of the day,[8] for which goal a strict AC dosing regimen is required. Non-AC dosing leads to sub-optimal acid suppression, resulting in less effective symptom control. Not surprisingly, sub-optimal dosing has been shown to be prevalent among poor responders to treatment.[2]

Diminished effectiveness of acid suppression due to sub-optimal dosing inevitably means reduced cost-effectiveness. This is because affected patients may require additional medication, such as antacids, as well as larger doses and more prolonged use of medications. Despite availability of generic omeprazole, on the whole PPIs are relatively expensive medications. The present study shows that they are prescribed in substantial quantities, and correspondingly, the economic implications of using them sub-optimally must be substantial.

On-demand treatment of PPI for GERD, in which the patient is allowed to take PPIs only when symptoms recur, is a proven patient-driven, cost-effective treatment policy.[8] The authors are of the opinion that such patients should also be instructed to take PPIs before meals 'on-demand' (ie AC dosing) for maximal therapeutic benefit. In this respect, on-demand therapy differs from taking PPIs 'as-needed' (PRN dosing). With the latter instruction, the patient takes a single dose of PPI anytime the need arises, without regard to meals and usually with the aim for immediate symptom relief. In a review of the pharmacological features of PPIs and their relevance to clinical practice, Welage[9] stressed that PPIs may take 3 to 4 days to achieve maximal acid suppression, thus a single dose of a PPI is not effective in immediate symptom relief. The author concluded that the "use of PPIs on an as-needed basis is not an effective means of inducing acid suppression or symptom relief".

We are unaware of similar studies of the effect of PPI dosing on peptic ulcer disease (PUD) healing and/or symptom control, as have been performed for GERD. Nonetheless, it seems reasonable that pharmacodynamics (PD) as well as PK considerations be taken into account, when formulating dosing advice. Inasmuch as optimal acid suppression is the key objective whenever PPIs are used (for GERD, PUD, helicobacter eradication, gastric protection for aspirin or NSAID users, or even ulcer like functional dyspepsia), it makes sound pharmacological sense to prescribe AC dosing for all patients.

Furthermore, we believe that one major reason underlying the medical profession's general unawareness of AC prescribing for PPIs is that such dosing has not been adequately emphasised by pharmaceutical companies (in their product inserts) or by academia. Hopefully, such instructions will be reviewed and updated in the future, and that based on PD as well as PK considerations, AC dosing will be stressed.

Gastroenterologists and pharmacists also have the opportunity and authority to promote AC dosing for PPIs. This audit shows that over 85% of non-AC PPI dosing was NS; the prescribing doctors simply did not specify the dosing time in relation to meals. With appropriate authorisation, pharmacists could alert patients on correct dosing by introducing AC dosing as default instructions for these drugs, or by issuing a separate advice leaflet. Similarly, gastroenterologists can bring this issue to the attention of their colleagues in the same and other specialties. Teaching and public institutes should promote awareness of this issue in the medical profession and the patient population. Patient education is crucial, as optimal dosing for PPIs eventually depends on patient compliance to the advice provided through the collective efforts of the medical profession.

Regarding limitations of the present study, we collected no data on the indications for which the PPIs were prescribed or the degree of symptom control achieved with the various dosing regimens. Moreover, there was no audit on patient compliance to AC or other dosing instructions. Therefore we are unable to co-relate the consequences of sub-optimal dosing on the various conditions for which they were prescribed.

We look forward to studying PPI dosing in greater detail in follow-up studies, which could look into the effect of dosing time (AC versus non-AC) on symptom control, patient preference and compliance. Possible changes in future prescribing behaviour of medical professionals, as a consequence of enhanced awareness of the significance of PPI dosing time, could also be studied.

Conclusions

The vast majority of PPIs are prescribed in a non-AC fashion, according to our audit in a large Hong Kong private hospital. We suggest rectification of this situation through the joint efforts of pharmaceutical companies, pharmacists, and the medical profession. We trust that this audit will arouse interest, and become a catalyst for further more in-depth and relevant studies in this area.

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Declaration

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