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The status of proton pump inhibitor use: a prescription survey of 45 hospitals in China

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ABSTRACT

Background: proton pump inhibitors (PPI) have been widely used in the clinic but inappropriate prescribing has also increased dramatically.

Objective: to describe the prescribing patterns and assess the appropriateness of the p rescribed PPI use in 45 hospitals in China.

Materials and methods: PPI prescriptions for non-hospitalized patients were collected from hospitals in Beijing, Chengdu, Guangzhou and Hangzhou of China over a 40-day period in 2016. These data were analyzed using the prescription number, proportion and economic indicators (defined daily dose system [DDD], defined daily cost [DDC] and drug utilization index [DUI]). The evaluation criteria of PPI use was based on *Martindale: The Complete Drug Reference*, *New Materia Medica* and drug instructions.

Results: in total, 357,687 prescriptions using oral PPI and 38,216 prescriptions using injectable PPI were assessed. The average age of PPI users was 53 years. The most commonly used oral PPI was rabeprazole, while the most common injectable PPI was pantoprazole. The DDD of oral rabeprazole and DDC of injectable rabeprazole were the highest. Meanwhile, only the DUI values of oral rabeprazole, lansoprazole and ilaprazole were less than 1.0. The clinical diagnosis of some users included well identified risky comorbidities such as kidney disease (2.9%). Furthermore, between 32.6% and 56.8% of the PPI prescriptions were used for inappropriate indications.

Conclusion: this survey demonstrated that PPI use was accompanied by unapproved indications and excessive dosages. Comprehensive measures are urgently needed to improve PPI use and reduce unnecessary drug costs.

Key words: Proton pump inhibitors. Prescription. Indications. Survey.

INTRODUCTION

Proton pump inhibitors (PPI) are essentially H^+-K^+-ATPase inhibitors. These are widely prescribed to treat acid-related diseases such as gastritis, peptic ulcer diseases (PUD), gastroesophageal reflux disease (GERD), gastrointestinal (GI) bleeding and *Helicobacter pylori (H. pylori)* infection (1,2). Moreover, PPI can be co-prescribed as gastro-protective drugs with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and anticoagulants, especially in elderly patients (3). The currently marketed PPIs in China include omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and ilaprazole. Inappropriate PPI use and the associated risks have dramatically increased over the last few decades (2,4-6). Emerging post-marketing studies have demonstrated that inappropriate PPI use has become a major clinical problem (2,7,8). Several case-control, cohort and meta-analyses studies have reported that PPI use increased the risk of various adverse effects including kidney disease (9-17). Thus, it is essential to determine the prescribing patterns and assess the appropriateness of the prescribed PPI, so that an

effective and rational follow-up plan can be implemented.

In the present survey, the PPI prescriptions of non-hospitalized patients from 45 hospitals in Beijing, Chengdu, Guangzhou and Hangzhou of China were collected. The data were subsequently analyzed using the number of prescriptions, the percentage, defined daily dose system (DDD), defined daily cost (DDC) and drug utilization index (DUI) (18). This study aimed to describe the prescribing patterns of PPI, analyze the variability among different PPI and evaluate the appropriateness of the prescribed PPI in hospitals in China.

MATERIALS AND METHODS

Data collection, inclusion criteria and evaluation standard

The present study was supervised by Professor Li Da-Kui. The following prescription information was collected: city, time, hospital code, prescription number, clinical department, drug generic name, drug specification, medication route, total amount of medicine taken, unit price, daily dosage, single dose, gender, age and diagnosis. The data was obtained from a project on prescription analysis that used the same criteria (19). The main aim was to analyze the status and trends of PPI use in China. More than 100 hospitals from eight metropolitan areas participated in the project every year. These hospitals provided data on prescriptions for each sample day to the research group. Forty sampling days per year were collected that consisted of three or four sampling days every month (19). This study was performed according to the guidelines of the World Medical Association and the Declaration of Helsinki. The Ethics Committee of the Institutional Review Board of our hospital approved the survey.

The 45 hospitals included in the study are three-A general hospitals from four metropolitan areas (Beijing, Chengdu, Guangzhou and Hangzhou) in China. These cities are located in the north, west, south, and east of China, respectively. Thus, the status of PPI use represented a wide coverage of the country. PPI prescriptions for non-hospitalized patients (outpatients and emergency patients) over a period of 40 days were collected in 2016. The PPI prescriptions without a diagnosis were excluded. The prescriptions were

divided into oral PPI prescriptions and injectable PPI prescriptions for the final analysis.

The defined daily dose (DDD) value for each form of PPI (oral or injectable dosage form) was recommended by the World Health Organization or drug instructions. The DDD value for PPI is equal to the ratio of the total doses of PPI (g) and the DDD value (g), the DDC value is equal to the ratio of the total sales of PPI and the DDD value, whereas the DUI value is equal to the ratio of the DDD value and the actual days of PPI use. As previously reported (18), the larger the DDD the higher the frequency of PPI prescription. This reflects the trends of PPI use, whereas the DDC value indicates the average daily cost of PPI use. A DUI value of more than 1.0 indicates that the actual dosage is higher than DDD, suggesting the use of an excess dose of PPI. The DUI value can be used as a standard to determine whether the dose is reasonable or not. The evaluation criteria for the indications of PPI use was based on *Martindale: The Complete Drug Reference* (35th edition, England), *New Materia Medica* (17th edition, China) and drug instructions.

Statistical analysis

The prescription information was processed using the Microsoft Access software and then exported to Microsoft Office Excel® 2007 (Microsoft Corp., Redmond, WA, USA) for statistical analysis.

RESULTS

In total, 395,903 cases of PPI prescriptions were finally included in the survey. The proportion of PPI prescriptions was 6.2% in Hangzhou but was lower in Chengdu (5.6%), Guangzhou (4.5%) and Beijing (3.5%). Six kinds of PPI were used in these hospitals including meprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and ilaprazole. The majority of the PPI prescriptions were via oral administration (90.4%) and the remaining were via injection (9.6%); 50.1% of patients were female and the average age of the PPI users was 53 years and the maximum age was 117 years. One percent of the users were < 18 years old, 35.1% were > 60 years old and 39.1% were aged > 40 years

and ≤ 60 years.

Variability among different PPI

With regard to PPI use in different cities, Guangzhou had the highest rate of PPI use (29.1%), followed by Hangzhou (27.5%), whereas the rate was similar in Beijing and Chengdu (Table 1). Among the oral dosage form of PPI (Table 1), rabeprazole was the most widely used (29.1%), followed by pantoprazole, lansoprazole, esomeprazole and omeprazole, whereas the lowest proportion was ilaprazole (1.4%). However, PPI use via injection showed a different trend, with the highest use of pantoprazole (4.7%), followed by omeprazole, lansoprazole, esomeprazole and rabeprazole (Table 1). There was no data with regard to the use of ilaprazole via injection.

Clinical diagnosis of PPI prescriptions

The approved indications for PPI use included GERD (20.2%), PUD (10.3%), *H. pylori* infection (5.9%) and gastrointestinal (GI) bleeds (1.5%) (Fig. 1). Among the PPI prescriptions, rabeprazole was primarily used to treat GERD, PUD and *H. pylori* infection, whereas pantoprazole was mainly used to treat GI bleeds. Moreover, the PPI prescriptions with a gastritis-related diagnosis and dyspepsia accounted for 34.3% and 4.3% of cases, respectively.

Risky comorbidities of PPI users

In recent years, the risks of PPI use have become a research hot topic. It has been reported that PPI use may be associated with kidney injury, pneumonia, bone fracture, dementia, vitamin B_{12} deficiency, iron deficiency and hypomagnesemia (9-17). According to our analysis, 2.9% of PPI users had kidney diseases, 2% had osteoporosis and 0.6% had pneumonia. In addition, smaller proportions of PPI users had these diseases in association with fractures, dementia, vitamin B_{12} deficiency, iron deficiency and hypomagnesemia.

PPI prescription in different clinical departments

PPI were most commonly used in the Department of Gastroenterology (40.1%) and Emergency Medicine (11.7%) (Fig. 2). A higher rate of PPI use was also found in other departments including General Internal Medicine (6.6%), Cardiology (6.5%) and Rheumatology (4.5%). These patients had more than one disease, including digestive tract diseases, or the prescribed PPIs were used for ulcer prevention due to the concomitant therapy with other gastro-erosive drugs.

DDD, DDC and DUI values of different PPI

We analyzed the DDD, DDC and DUI values of different PPI. Table 2 shows that the DDD value of oral rabeprazole and the DDC value of injectable rabeprazole were the highest, while the lowest DDD value was obtained for injectable rabeprazole and the minimum value of DDC was for oral omeprazole. Among the DUI values of PPI, only oral rabeprazole, lansoprazole and ilaprazole were less than 1.0.

DISCUSSION

PPI are among the most commonly prescribed drugs worldwide. Recent data have shown that the proportion of PPI users has increased from 0.2% in 1990 to 15.0% in 2014, in the UK (20). There is also evidence showing inappropriate PPI use, without approved indications in general medical wards ranging from 40% to 81% (21). Moreover, there are emerging potential adverse effects or risks induced by PPI abuse or in conjunction with other drugs (4,22,23). The overuse of PPI not only leads to undesirable outcomes but there is also a significant high cost (24). Thus, conducting a survey to assess the present status of PPI prescription in China is urgent and meaningful.

In this study, the clinical trends of PPI use varied greatly. The oral form of rabeprazole, pantoprazole and lansoprazole were the most commonly used PPI. Among the injectable forms, pantoprazole and omeprazole were the most commonly used. The PPI were mostly prescribed in the departments of Gastroenterology and Emergency Medicine, which may

be due to the main application of PPI in digestive system diseases, based on their indications. However, high rates of PPI use were also found in the General Internal Medicine, Cardiology and Rheumatology departments. The rise of gastro-erosive drugs consumption (such as NSAIDs) and ageing of the patients in these departments could partly explain the increased of PPI use.

Clinical diagnosis is the foundation for treating diseases and forms the basis of the selection of appropriate medications to treat certain diseases, while irrational drug use can also be screened. In our survey, the completely approved indications for PPI use included GERD, PUD, *H. pylori* infection and GI bleeds. NSAIDs (6.0%) use was also reported in the high-risk users. Moreover, the diagnosis of gastritis (34.3%) and dyspepsia (4.3%) were a vague diagnostic description or symptom and were uncertain indications for PPI use. Unfortunately, we could not obtain evidence from the endoscopy or biopsy samples or other examinations to rule out unreasonable PPI use. Based on the above data, between 32.6% and 56.8% of PPI prescriptions were considered as off-label medications. These data were similar to those reported in other surveys (21,24).

The DDC results showed that the highest average daily costs of PPI were injectable rabeprazole (mostly used in Guangzhou), followed by injectable esomeprazole (mostly used in Beijing). Thus, indicating that these patients paid a high price when these drugs were prescribed. The lowest DDC value was for oral omeprazole, suggesting that it has a price advantage for clinical use. However, omeprazole was one of the least used oral PPIs in this survey. There is little research evidence to prove any significant differences among these PPI for the treatment of the related diseases. Hence, the above data suggests an inappropriate drug selection when prescribing PPI. However, this situation may also be related to the local health insurance reimbursement in different areas and therefore, the relevant departments should probe this issue. The DUI data showed that injectable rabeprazole, injectable lansoprazole and both forms of pantoprazole, esomeprazole, and omeprazole were used in excessive doses in patients. This may be related to medical advice errors that require effective intervention from the doctors, nurses or pharmacists.

Data on the risky comorbidities were also noteworthy. Our data showed that some PPI users had underlying risky comorbidities such as renal diseases (2.9%) and osteoporosis (2%) (25,26). PPI may trigger acute interstitial nephritis, which is a severe event associated with acute kidney injury. Besides, PPI may reduce calcium absorption, interfere with bone metabolism and increase the risk of osteoporosis. Thus, doctors should consider these conditions when prescribing PPI in these special cases. The data of the duration of PPI treatment could not be obtained as the data were a sample of prescriptions over a 40-day period and we did not know whether PPI had been prescribed before or would be prescribed later. This was also a limitation of the study. Furthermore, we could not obtain the information on the pathological examinations, laboratory indicators or other diagnostic details, in order to ensure the accuracy of the diagnosis of acid-related diseases or gastrointestinal diseases. In addition, our data were obtained according to the difference of prescription numbers, which could not be fully distinguished from patients.

Even though, the four selected areas in this survey were representative (19), the results partly reflect the status of PPI use in China. The increase in PPI consumption and decrease in indication might translate to a belief that the elderly and/or polymedicated patients must be treated with PPI. This generalized overuse of PPI and the high rate of inappropriate prescriptions demonstrates a lack of concern for optimizing PPI use. More efforts are needed to ensure the choice of suitable PPI and promote the rational use. First, it is important to regularly reassess the need for ongoing treatment with PPI and how the risks can be reduced when prescribing PPI. Second, PPI over-use should be controlled by limiting the appropriateness of reimbursement, over-prescription and improving the distribution of therapeutic recommendation guidelines (27). Third, more studies should define the appropriate indications of PPI use, investigate the exact causality between risk and PPI use and also develop alternate management options for acid peptic diseases (24,28). As an alternative, H_2-receptor antagonists may be used to suppress gastric acid production. It is worth mentioning that reducing PPI use may come from the lifestyle changes, including the avoidance of coffee, alcohol, spicy and fatty meals, smoking and a

supine position after eating. This is especially important for users with gastric acid-related diseases or symptoms (29). Finally, we should also limit the therapy to the lowest effective dosage and not discontinue PPI use when there is clear evidence for its requirement.

CONCLUSION

There was a significant increase in both PPI use and the rate of PPI inappropriate prescriptions in our study, which has become a matter of public interest. The present survey provides valuable data with regard to the variability of different PPI as well as the inappropriate indications and the use of excessive doses. PPI use needs to be improved and unnecessary drug spending reduced.

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327 **Table 1. The prescription number and proportion of different PPI in different cities**

Dosage form	*Beijing*	*Chengdu*	*Guangzhou*	*Hangzhou*	*Sum.*
Oral rabeprazole	33,941 (8.6%)	23,873 (6.0%)	30,805 (7.8%)	26,718 (6.7%)	115,337 (29.1%)
Injectable rabeprazole	0 (0.0%)	0 (0.0%)	1,345 (0.3%)	5 (0.0%)	1,350 (0.3%)
Oral pantoprazole	12,507 (3.2%)	11,918 (3.0%)	20,808 (5.3%)	28,917 (7.3%)	74,150 (18.7%)
Injectable pantoprazole	4,765 (1.2%)	3,490 (0.9%)	918 (0.2%)	9,292 (2.3%)	18,465 (4.7%)
Oral lansoprazole	4,004 (1.0%)	28,535 (7.2%)	24,475 (6.2%)	10,214 (2.6%)	67,228 (17.0%)
Injectable lansoprazole	775 (0.2%)	599 (0.2%)	774 (0.2%)	1,082 (0.3%)	3,230 (0.8%)
Oral esomeprazole	14,339 (3.6%)	11,600 (2.9%)	16,950 (4.3%)	14,035 (3.5%)	56,924 (14.4%)
Injectable esomeprazole	1,919 (0.5%)	14 (0.0%)	860 (0.2%)	164 (0.0%)	2,957 (0.7%)
Oral omeprazole	9,609 (2.4%)	5,250 (1.3%)	9,468 (2.4%)	14,324 (3.6%)	38,651 (9.8%)
Injectable omeprazole	3,677 (0.9%)	229 (0.1%)	4,082 (1.0%)	4,226 (1.1%)	12,214 (3.1%)
Oral ilaprazole	0 (0.0%)	685 (0.2%)	4,712 (1.2%)	0 (0.0%)	5,397 (1.4%)
Sum.	85,536 (21.6%)	86,193 (21.8%)	115,197 (29.1%)	108,977 (27.5%)	395,903 (100.0%)

328

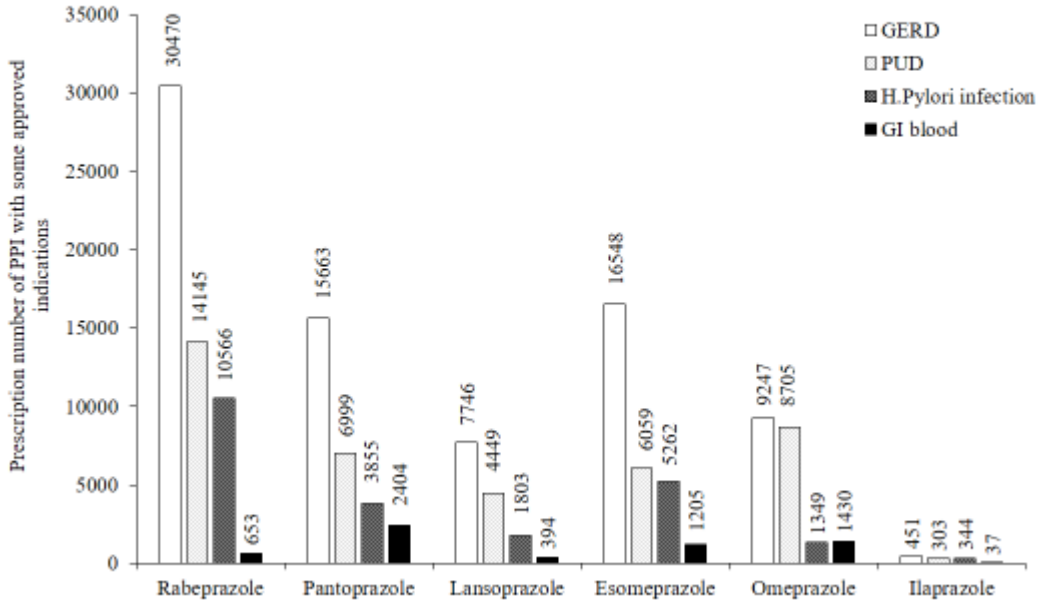
329 PPI: proton pump inhibitors.

330 **Table 2. DDD, DDC and DUI values of different PPI**

Dosage form of PPI	*Total doses (g)*	*Medication days (d)*	*Total sales (dollar)*	*DDD (mg)*	*DDDs*	*DDC (dollar)*	*DUI*
Oral rabeprazole	29,902.2	1,463,298	17,426,769	20	1,495,111	11.7	1.0
Oral pantoprazole	49,008.4	961,078	9,124,989	40	1,225,209	7.4	1.3
Oral lansoprazole	31,717.7	1,069,420	7,126,307	30	1,057,258	6.7	1.0
Oral esomeprazole	23,737.8	720,459	12,521,192	30	791,259	15.8	1.1
Oral omeprazole	16,444.1	629,089	4,354,944	20	822,204	5.3	1.3
Oral ilaprazole	369.2	53,860	1,245,244	10	18,462	67.4	0.3
Injectable rabeprazole	30.4	1,347.5	254,160	20	1,521	167.1	1.1
Injectable pantoprazole	1,269.6	21,881	1,527,778	40	31,739	48.1	1.5
Injectable lansoprazole	144.9	3,535	335,550	30	4,829	69.5	1.4
Injectable esomeprazole	166.8	3,341	519,596	30	5,560	93.5	1.7
Injectable omeprazole	656.7	13,964	950,181	20	16,418	57.9	1.2

331

332 DDC: defined daily cost; DDDs: defined daily dose system; DUI: drug utilization index; PPI:
333 proton pump inhibitors.



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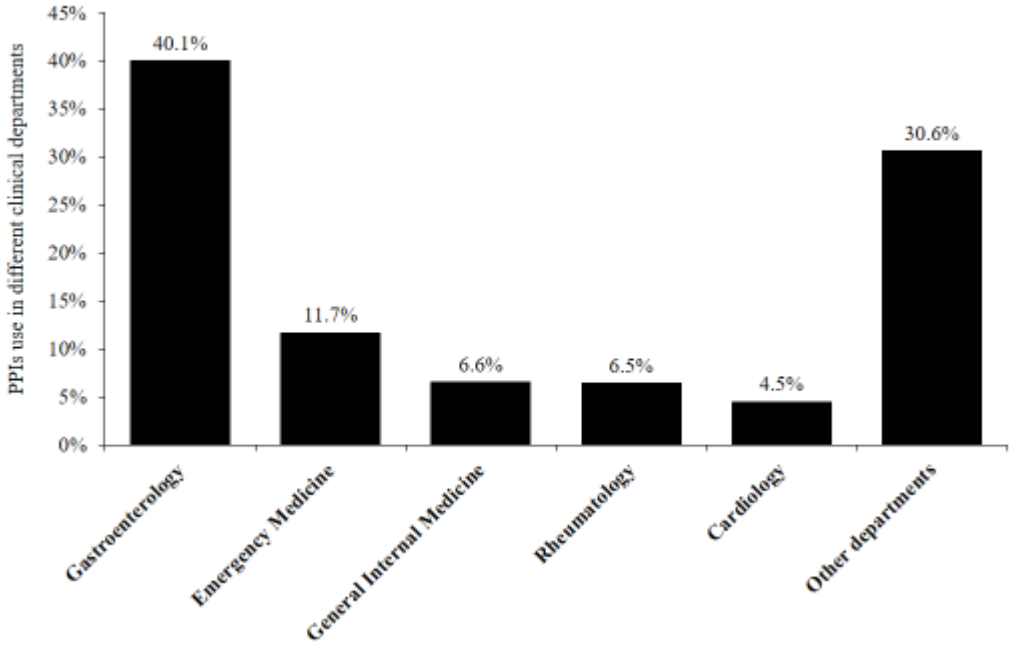
336 Fig. 1. Prescription number of different PPI with some approved indications. GERD:
337 gastroesophageal reflux disease; GI: gastrointestinal bleeding; *H. pylori*: *Helicobacter*
338 *pylori*; PPI: proton pump inhibitors; PUD: peptic ulcer diseases.



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340 Fig. 2. PPI use in different clinical departments. PPI: proton pump inhibitors.

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