

Poor awareness of preventing aspirin-induced gastrointestinal injury with combined protective medications

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Abstract

AIM: To investigate prescribing pattern in low-dose aspirin users and physician awareness of preventing aspirin-induced gastrointestinal (GI) injury with combined protective medications.

METHODS: A retrospective drug utilization study was conducted in the 2nd Affiliated Hospital, School of Medicine, Zhejiang University. The hospital has 2300 beds and 2.5 million outpatient visits annually. Data mining was performed on all aspirin prescriptions for outpatients and emergency patients admitted in 2011. Concomitant use of proton-pump inhibitors (PPIs),

histamine 2-receptor antagonists (H2RA) and mucoprotective drugs (MPs) were analyzed. A defined daily dose (DDD) methodology was applied to each MP. A further investigation was performed in aspirin users on combination use of GI injurious medicines [non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids and clopidogrel and warfarin] or intestinal protective drugs (misoprostol, rebamipide, teprenone and gefarnate). Data of major bleeding episodes were derived from medical records and adverse drug reaction monitoring records. The annual incidence of major GI bleeding due to low-dose aspirin was estimated for outpatients.

RESULTS: Prescriptions for aspirin users receiving PPIs, H2RA and MPs ($n = 1039$) accounted for only 3.46% of total aspirin prescriptions ($n = 30\ 015$). The ratios of coadministration of aspirin/PPI, aspirin/H2RA, aspirin/MP and aspirin/PPI/MP to the total aspirin prescriptions were 2.82%, 0.12%, 0.40% and 0.12%, respectively. No statistically significant difference was observed in age between patients not receiving any GI protective medications and patients receiving PPIs, H2RA or MPs. The combined medication of aspirin and PPI was used more frequently than that of aspirin and MPs (2.82% vs 0.40%, $P < 0.05$) and aspirin/H2RA (2.82% vs 0.12%, $P < 0.05$). The values of DDDs of MPs in descending order were as follows: gefarnate, hydrotalcite > teprenone > sucralfate oral suspension > L-glutamine and sodium gualenate granules > rebamipide > sucralfate chewable tablets. The ratio of MP plus aspirin prescriptions to the total MP prescriptions was as follows: rebamipide (0.47%), teprenone (0.91%), L-glutamine and sodium gualenate granules (0.92%), gefarnate (0.31%), hydrotalcite (1.00%) and sucralfate oral suspension (0.13%). Percentages of prescriptions containing aspirin and intestinal protective drugs among the total aspirin prescriptions were: rebamipide (0.010%), PPI/rebamipide (0.027%), teprenone (0.11%), PPI/teprenone (0.037%), gefarnate (0.017%), and PPI/gefarnate (0.013%). No prescriptions were found containing coadministration of aspirin and other NSAIDs. Among the 3196 prescriptions containing aspirin/clopidogrel,

3088 (96.6%) prescriptions did not contain any GI protective medicines. Of the 389 prescriptions containing aspirin/corticosteroids, 236 (60.7%) contained no GI protective medicines. None of the prescriptions using aspirin/warfarin ($n = 22$) contained GI protective medicines. Thirty-five patients were admitted to this hospital in 2011 because of acute hemorrhage of upper digestive tract induced by low-dose aspirin. The annual incidence rates of major GI bleeding were estimated at 0.25% for outpatients taking aspirin and 0.5% for outpatients taking aspirin/warfarin, respectively.

CONCLUSION: The prescribing pattern of low-dose aspirin revealed a poor awareness of preventing GI injury with combined protective medications. Actions should be taken to address this issue.

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Key words: Low-dose aspirin; Gastrointestinal injury; Small bowel injury; Drug utilization; Prescribing patterns; Combined medications; Proton-pump inhibitors; Histamine 2-receptor antagonists; Mucoprotective drugs; Defined daily dose

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INTRODUCTION

We read with great interest in the study by Mizukami *et al*^[1], who evaluated the influence of taking low-dose aspirin for 4 wk on small intestinal injury and examined the preventive effect of rebamipide. The results showed that long-term aspirin induced small bowel damage (7 cases with a mucosal break at 4 wk on the ileum and 1 on the jejunum at 4 wk among 11 healthy subjects) and rebamipide significantly prevented this damage, and it may be a candidate drug for treating aspirin-induced small bowel complications.

Long-term low-dose aspirin (75-325 mg) has been increasingly prescribed to elderly patients for primary and secondary prevention of cardiovascular and cerebral diseases. Nonetheless, aspirin's efficacy in such disease prevention is limited by the risk of gastrointestinal (GI) injury. Aspirin treatment can increase the GI risk by 2-fold in middle-aged patients without a prior history of peptic ulcer and without using concomitant drugs^[2]. Compared

with low-dose aspirin monotherapy, the risk of upper GI injury increased when low-dose aspirin was used in combination with clopidogrel [relative risk (RR), 2.08], oral anticoagulants (RR, 2.00), nonsteroidal antiinflammatory drugs (NSAIDs) (RR, 2.63), or high-dose oral corticosteroids (RR, 4.43)^[3]. While the aspect on preventing upper GI complications induced by aspirin^[4-7] was emphasized, the study by Mizukami *et al*^[1] has reminded us of attaching equal importance to prevention of small bowel injury. We have investigated the status of prescribing pattern of low-dose aspirin in an attempt to recommend the use of combined therapy of proton-pump inhibitors (PPIs), histamine 2-receptor antagonists (H2RA) or mucoprotective drugs (MPs) to prevent aspirin-induced GI injuries. We would discuss and share our perspectives below.

MATERIALS AND METHODS

The prescribing pattern of low-dose aspirin was investigated from the perspective of concomitant use of PPIs, H2RA or MPs in the 2nd Affiliated Hospital, School of Medicine, Zhejiang University. The hospital has 2300 beds and 2.5 million outpatient visits annually. Prescription data was obtained from the hospital information system and processed with Visual FoxPro 9.0. Statistical analysis was performed on the number of prescriptions with aspirin, aspirin/PPI, aspirin/H2RA, aspirin/MP, aspirin/PPI/MP and aspirin/H2RA/MP for outpatients and emergency patients admitted in 2011.

Oral PPIs included omeprazole (or magnesium salt), pantoprazole (or sodium salt), rabeprazole, lansoprazole and esomeprazole magnesium. Intravenous PPIs included omeprazole sodium, pantoprazole sodium and esomeprazole sodium. MPs included teprenone, L-glutamine and sodium gualenate granules (Marzulene-S[®]), misoprostol, rebamipide, gefarnate, sucralfate oral suspension, hydro-talcite and sucralfate chewable tablets.

Annual amount of each MP consumed was calculated. A defined daily dose (DDD) methodology was applied^[8]. The DDD value of each MP was derived from its package insert. DDDs and daily expenditure were estimated using the following equations:

$$\text{DDD} = \frac{\text{Total dosage (amount of drug consumed)}}{\text{DDD}}$$

$$\text{Daily expenditure} = \frac{\text{Overall expenditure}}{\text{DDD}}$$

A further investigation was performed in aspirin users taking GI injurious medicines (NSAIDs, corticosteroids, clopidogrel and warfarin) or intestinal protective drugs (misoprostol, rebamipide, teprenone and gefarnate) which prevented small bowel injury induced by low-dose aspirin or other NSAIDs in human^[1,9-12] or rats^[13,14]. Data of major bleeding episodes were derived from the medical records and adverse drug reaction monitoring records. The annual incidence of major GI bleeding due to low-dose aspirin was estimated for outpatients.

Age differences between patient groups were tested using Student's *t* test. χ^2 test was used for comparisons of ratios of prescriptions with combined aspirin and other drugs to the total aspirin prescriptions. Difference

was considered statistically significant at $P < 0.05$ for all analyses.

RESULTS

Prescriptions for aspirin users receiving PPIs, H2RA and MPs ($n = 1039$) only accounted for 3.46% of total aspirin prescriptions ($n = 30\,015$). Among 1039 patients, there were 924 (88.5%) patients on 100 mg aspirin, 108 (10.8%) patients on 200 mg aspirin and 7 (0.7%) patients on 300 mg aspirin. No statistically significant difference in age was observed between patients not receiving any GI protective medications ($n = 28\,976$, aged 63.3 ± 12.4 years) and patients receiving PPIs, H2RA or MPs ($n = 1039$, 61.8 ± 17.9 years) ($P > 0.05$).

Coadministration of aspirin/PPI, aspirin/H2RA, aspirin/MP and aspirin/PPI/MP accounted for 2.82%, 0.12%, 0.40% and 0.12%, respectively of the total aspirin prescriptions (Table 1). Combined use of aspirin/PPI was more frequent than that of aspirin/MP (2.82% *vs* 0.40%, $P < 0.05$) and aspirin/H2RA (2.82% *vs* 0.12%, $P < 0.05$). Combined therapy of aspirin and two MPs was not found among the prescriptions.

Prescriptions with combination use of pantoprazole, esomeprazole and rabeprazole accounted for 82.6% of all prescriptions containing aspirin/oral PPIs. Omeprazole only accounted for 17.1%.

Pharmacoeconomic indices of MPs for outpatients are listed in Table 2. The values of DDDs of MPs in descending order were as follows: gefarnate, hydrotalcite > teprenone > sucralfate oral suspension > L-glutamine and sodium gualenate granules > rebamipide > sucralfate chewable tablets.

The total dosage (amount of drug consumed) of misoprostol in 2011 was 564.6 mg. However, misoprostol was prescribed for termination of early pregnancy in combination with mifepristone instead of indication for reducing the risk of NSAIDs-induced GI injury. No combined use of misoprostol and aspirin was found among the prescriptions.

The ratio of amount of MP comedicated with aspirin to total amount of MP consumed in 2011 was 0.47% (rebamipide), 0.91% (teprenone), 0.92% (marzulene-S), 0.31% (gefarnate), 1.00% (hydrotalcite) and 0.13% (sucralfate oral suspension), respectively.

Percentages of prescriptions containing aspirin and intestinal protective drugs to the total aspirin prescriptions were: aspirin/rebamipide ($n = 3$, 0.010%), aspirin/PPI/rebamipide ($n = 5$, 0.027%); aspirin/teprenone ($n = 33$, 0.11%), aspirin/PPI/teprenone ($n = 11$, 0.037%), aspirin/gefarnate ($n = 5$, 0.017%), and aspirin/PPI/gefarnate ($n = 4$, 0.013%).

No prescriptions were found containing coadministration of low-dose aspirin and other NSAIDs. There were 3196 prescriptions with concomitant use of aspirin/clopidogrel in 2011. However, only 108 (3.4%) prescriptions contained aspirin/clopidogrel/PPI ($n = 101$), aspirin/clopidogrel/MP ($n = 4$) and aspirin/clopidogrel/PPI/MP ($n = 3$). None of 3088 (96.6%) prescriptions

Table 1 Concomitant use of proton-pump inhibitors, H2-receptor antagonists or mucoprotective drugs in patients taking low-dose aspirin

Drug name	Number of prescriptions	Percentage of prescriptions with combination therapy to total aspirin prescriptions (%)
H2RA	36	0.12 ^a
Oral PPIs	708	2.36
Pantoprazole	342	1.14
Esomeprazole	157	0.52
Omeprazole	121	0.40
Rabeprazole	85	0.28
Lansoprazole	3	0.01
i.v. PPIs	139	0.46
Pantoprazole sodium	132	0.44
Omeprazole sodium	7	0.02
MPs	120	0.40 ^c
Hydrotalcite	43	0.14
Teprenone	33	0.11
Marzulene-S	25	0.083
Sucralfate	11	0.037
Gefarnate	5	0.017
Rebamipide	3	0.010
Misoprostol	0	0
PPI/MPs	36	0.12
Teprenone	11	0.037
Hydrotalcite	9	0.030
Rebamipide	5	0.017
Marzulene-S	4	0.013
Gefarnate	4	0.013
Sucralfate	3	0.010
Misoprostol	0	0

^a $P < 0.05$ *vs* oral proton-pump inhibitors (PPIs) plus i.v. PPIs; ^c $P < 0.05$ *vs* oral PPIs plus i.v. PPIs. MPs: Mucoprotective drugs; H2RA: H2-receptor antagonists.

Table 2 Pharmacoeconomic indices of mucoprotective drugs for outpatients in 2011

Drug name	Total dose (g)	DDD (g)	DDDs	Overall expenditure (CNY)	Daily expenditure (CNY)
Gefarnate	14 252	0.15	95 013	312 000	3.3
Hydrotalcite chewable tablet	282 842	3	94 280	557 000	7.4
Teprenone	11 345	0.15	75 633	380 000	5.0
Sucralfate oral suspension	459 648	8	57 456	444 000	7.7
Marzulene-S	89 880	2	44 940	250 000	5.6
Rebamipide	11 195	0.3	37 316	214 000	5.8
Sucralfate chewable tablet	13 950	4	3488	3600	1.0

MPs: Mucoprotective drugs; DDD: Defined daily dose; CNY: China Yuan.

contained any GI protective medications. PPIs coadministered with aspirin and clopidogrel included: oral pantoprazole ($n = 58$), esomeprazole ($n = 32$), i.v. pantoprazole ($n = 9$) and rabeprazole ($n = 2$). No prescriptions were found containing aspirin/clopidogrel/omeprazole.

There were 389 prescriptions with concomitant use of aspirin/corticosteroids (prednisone, methylprednisolone and dexamethasone) in 2011. However, only 153 (39.3%) prescriptions contained aspirin/corticosteroid/

PPI ($n = 148$), aspirin/ corticosteroid/MP ($n = 4$) and aspirin/corticosteroid/PPI/MP ($n = 1$). Two hundred and thirty-six prescriptions (60.7%) did not contain any GI protective medications.

There were 22 prescriptions with concomitant use of aspirin/warfarin in 2011. Again, none of these prescriptions contained GI protective medications.

There were 35 patients admitted to this hospital because of acute hemorrhage of upper digestive tract induced by low-dose aspirin in 2011. The annual incidence rates of major GI bleeding were estimated at 0.25% for outpatients on aspirin and 0.5% for outpatients on aspirin/warfarin, respectively. For example, an 81-year-old male patient with coronary artery disease treated by percutaneous coronary interventions and arterial embolism of lower limb, received aspirin (100 mg, q.d.), warfarin (3 mg, q.d.), clopidogrel (75 mg, q.d.) and beraprost sodium (20 μ g, t.i.d.) but without concomitant use of any PPIs or MPs. Two weeks later he was sent to the Emergency Center because of GI hemorrhage. Aspirin therapy was stopped and the patient was treated with i.v. pantoprazole. Five days later, he was discharged and continued to take oral pantoprazole (40 mg, q.d.) and rebamipide (0.1 g, t.i.d.) plus warfarin and clopidogrel. No adverse GI event was observed.

DISCUSSION

Yamamoto *et al.*^[5] examined the effects of gastroprotective drugs on aspirin-related gastroduodenal toxicity in 530 patients who had taken low-dose aspirin for 1 mo or more. Use of a PPI alone was significantly more protective against bleeding (9.3% *vs* 2.1%, $P < 0.01$) and mucosal injury (49.1% *vs* 18.6%, $P < 0.01$) than non-use of any gastroprotective medicine. Among the background characteristics, such as *Helicobacter pylori* infection, concomitant use of anticoagulants, anti-platelet agents, NSAIDs and PPI, a bleeding history, age and gender, only the co-administration of a PPI was found significantly associated with reduced bleeding events. Patients taking any medicine PPI, H2RA, MP, PPI (or H2RA) plus MP showed significantly better outcomes with respect to mucosal injury as compared with the patients not receiving any gastroprotective medication.

Our study indicated that only 3.46% of the patients taking low-dose aspirin received concurrent therapy of PPI, H2RA and MPs. Thus it is imperative to enhance the awareness of preventing GI injury induced by low-dose aspirin among both physicians and patients.

The combined therapy of aspirin and PPI was more frequently used than that of aspirin and MPs (2.82% *vs* 0.40%, $P < 0.05$) and aspirin/H2RA (2.82% *vs* 0.12%, $P < 0.05$) in this hospital and it may be due to the more potent effects of PPIs in prevention of NSAIDs-related GI injuries^[15]. However, Nema *et al.*^[7] observed that the healing rate of gastroduodenal ulcers during continuous use of low-dose aspirin was higher than 80% in both the PPI group and the H2RA group, with no significant difference between the two groups. Nakashima *et al.*^[16] con-

cluded that H2RA may be the most beneficial drug for both the prevention and treatment of low-dose aspirin-induced peptic ulcers, in which it has the similar anti-ulcer effects to PPIs, but with lower cost and fewer adverse effects as compared with PPIs and prostaglandins.

Concomitant use of NSAIDs, corticosteroids, clopidogrel or anticoagulants increases GI risk further in patients on low-dose aspirin^[2-4]. A meta-analysis by Lanas *et al.*^[4] showed that the risk for GI bleeding in aspirin users increased with concomitant use of clopidogrel and anticoagulant therapies, but decreased in patients who took PPIs. Astoundingly, our investigation showed that 96.6% of patients on aspirin plus clopidogrel, 60.7% of patients on aspirin plus oral corticosteroids and 100% of patients on aspirin plus warfarin did not receive any GI protective medications.

The anti-platelet effect of clopidogrel was activated by biotransformation *via* CYP2C19 and CYP3A4. Different PPIs have different effects on CYP2C19. It has been generally acknowledged that drug interaction between omeprazole and clopidogrel was of clinically significance and can reduce the efficacy of clopidogrel^[17]. Pantoprazole, esomeprazole and rabeprazole were alternatives^[18-20]. Coadministration of aspirin, clopidogrel and omeprazole was not observed in this study, indicating that this hospital is good at clopidogrel therapy management.

DDDs values of seven mucoprotective drugs were compared. Gefarnate's DDDs ranked first and this result may be associated with its relatively low price. Teprenone's DDDs ranked second. Murakami *et al.*^[21] concluded that the effects of teprenone on aspirin-induced gastric ulcers in rats were more potent and more definite than those of gefarnate. Fang *et al.*^[14] reported that teprenone (15.63 mg/kg daily) and gefarnate (31.25 mg/kg daily) can exert protective effects against the intestinal injury induced by NSAIDs in rats. Niwa *et al.*^[12] found that teprenone (300 mg/d) reduced diclofenac-induced gastric and small intestinal injuries in 10 healthy volunteers ($P < 0.05$). Shiotani *et al.*^[22] reported that 1 wk administration of low-dose aspirin to 20 healthy volunteers was associated with visible small bowel damage in the majority of users whereas teprenone (150 mg/d) could not prevent aspirin-induced small bowel injury. The inconsistent findings about the preventive effects of teprenone against small intestinal injury may be associated with the dosage of teprenone, sample size of clinical trials and species differences. Although gefarnate used 50 mg twice daily was inferior to lansoprazole at 15 mg daily in reducing the risk of gastric or duodenal ulcer recurrence in patients with a definite history of gastric or duodenal ulcers who required long-term low-dose aspirin therapy^[23], the proven effects of gefarnate in prevention of small intestinal injury induced by NSAIDs in rats provoked further investigations on whether gefarnate could prevent small intestinal injury in aspirin users.

Sucralfate is proved to have protective effects against NSAID-associated ulcer due to the enhanced prostaglandin synthesis, increased mucus secretion, suppression of pro-inflammatory cytokines such as tumor necrosis

factor- α (TNF- α), and induction of constitutive nitric oxide synthase as well as its antioxidant capability.^[24] Although it had the lowest daily expenditure, sucralfate chewable tablets had the lowest DDDs value. The DDDs value of sucralfate oral suspension was 16 times more than that of sucralfate chewable tablets, although oral suspension had a higher daily expenditure than chewable tablets. In this investigation, we observed that some patients swallowed the chewable tablets directly without chewing, and this implies that sucralfate suspension has a better medication compliance than chewable tablets.

Misoprostol exerts a protective effect on the gastrointestinal mucosa by increasing mucus and bicarbonate ion secretion as well as mucosal blood flow. In addition, it inhibits acid secretion. Watanabe *et al*^[9] reported that misoprostol 200 μg 4 times a day could effectively prevent aspirin-induced small intestinal injuries. However, drug compliance of misoprostol was not good due to its side effects and dosing frequency. In clinical trials, misoprostol-induced diarrhoea occurred in approximately one-tenth of the patients despite that it was usually mild and self-limiting. Donnelly *et al*^[25] conducted a double-blind placebo-controlled parallel group endoscopic study in 32 healthy volunteers over 28 d and concluded that low-dose misoprostol 100 μg daily can prevent the gastric mucosal injury induced by aspirin 300 mg daily without causing identifiable adverse effects. However, many physicians seem unaware of misoprostol use at such a low-dose. Off-label use of misoprostol (Cytotec[®], Piramal Healthcare Ltd., United Kingdom) is very common in China. In this investigation, all of Cytotec[®] was prescribed for termination of early pregnancy in combination with mifepristone. Thus misoprostol was eliminated by the Drug and Therapeutics Committee of this hospital in September 2011.

Rebamipide provides mucoprotective effect by inducing the production of intracellular prostaglandins and epidermal growth factor, improving blood flow, suppressing increases in permeability, scavenging free radicals and exerting anti-inflammatory effect^[1]. Yamamoto *et al*^[5] reported that in the patients taking rebamipide concomitantly with PPIs, aspirin-induced gastroduodenal mucosal injuries occurred less frequently than in those taking PPIs plus MPs other than rebamipide (14.8% *vs* 38.1%, $P < 0.01$). From this viewpoint, rebamipide had an obvious advantage over other MPs. Mizukami *et al*^[1] proved that rebamipide could prevent effectively aspirin-induced small bowel injury. If the exciting finding of this research can be applied to routine clinical practices, good clinical outcomes would be anticipated in patients taking low-dose aspirin.

Our investigation indicated a 0.25% incidence of upper GI bleeding in the low-dose aspirin users, a value nearly four times that of the documented baseline rate of 0.06% noted for the general population without medications or conditions predisposing to bleeding^[26], suggesting that low-dose aspirin users did have a relative higher risk of GI injury.

Physician education and computer alert were proved

to improve targeted use of gastroprotection among NSAID users^[27]. The poor awareness of preventing aspirin-induced GI injury with combined protective medications has attracted the attention of the Drug and Therapeutics Committee of this hospital. Actions to address this issue include academic lectures and computer alert to encourage prescriptions of GI protecting agents, a multi-disciplinary team building and initiation of risk-benefit long-term study on the association between increase in expenditure of GI protecting agents and outcomes such as significant reduction in hospital admissions/stays related to GI bleeding.

In conclusion, the study of Mizukami *et al*^[1] inspired us to perform this retrospective drug utilization study on the prescribing pattern of low-dose aspirin from the perspective of combined therapy in a large university teaching hospital in China. The results of our survey indicated the poor awareness of preventing gastric and small intestinal injury in patients taking low-dose aspirin with combined protective medications. Good clinical outcomes would be anticipated in aspirin users, especially in patients with a high risk of GI injury, given that the importance of administration of gastroduodenal protective PPIs and intestinal protective rebamipide as well as other GI mucoprotectives is being recognized.

COMMENTS

Background

Low-dose aspirin is currently recommended for the secondary prevention of cardiovascular and cerebral diseases. However, gastroduodenal mucosal injury may be induced by aspirin and concomitant use of non-steroid anti-inflammatory drugs, corticosteroids, clopidogrel or anticoagulants further increases gastrointestinal (GI) risk in patients taking low-dose aspirin. Concomitant use of proton-pump inhibitors (PPIs), histamine 2-receptor antagonists (H2RA) and mucoprotective drugs (MPs) with aspirin can help prevent GI injuries. Recently, aspirin-induced small bowel injuries have attracted clinical attention and preventive effects of some MPs have been observed. This may enhance the awareness of preventing aspirin-induced GI injury with combined protective medication in clinical practice.

Research frontiers

A retrospective drug utilization study on prescribing pattern of low-dose aspirin from the perspective of combination therapy was conducted in a large university teaching hospital of China. Clinical awareness of preventing aspirin-induced GI injury with combined protective medications was evaluated systematically.

Innovations and breakthroughs

The ratio of prescriptions for aspirin users receiving PPIs, H2RA and MPs to the total aspirin prescriptions was revealed for the first time. The survey indicated a poor awareness of preventing gastric and small intestinal injury in patients taking low-dose aspirin with combined protective medications. Combined use of GI injurious medicines or intestinal protective drugs in aspirin users was investigated. The annual incidence of major GI bleeding due to low-dose aspirin was also estimated in the outpatients admitted to the hospital in 2011. Additionally, a defined daily dose (DDD) methodology was applied to study the prescription pattern.

Applications

The findings of the study will enhance the awareness of preventing aspirin-induced GI injury with combined protective medications from physicians, pharmacists and nurses. Good clinical outcomes would be anticipated in aspirin users, especially in patients with a high risk of GI injury, as the importance of gastroduodenal protective PPIs and intestinal protective rebamipide as well as other MPs is being recognized. Actions should be taken such as encouraging prescription of GI protective agents, building a multi-disciplinary team and initiating a risk-benefit long-term study on the association between increase in

expenditure of GI protective agents and outcomes such as significant reduction in hospital admissions/stays related to GI bleeding.

Terminology

The DDD, a statistical measure of drug consumption, is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs value is determined by the formula: DDDs = annual consumption of a drug/drug DDD value. Higher DDDs value means that the drug is prescribed more frequently. Drug utilization studies aim to evaluate the factors related to the prescription, dispensation, administration and intake of medicines and its associated events (either beneficial or adverse).

Peer review

This is a very relevant piece of work summarizing the prescription pattern of low-dose aspirin. Combination use of GI injurious medicines or intestinal protective drugs in aspirin users was also investigated. Based on retrospective data obtained from large number of patients in China, the authors concluded that there is a need for increasing the awareness of preventing aspirin-induced GI injury by concomitant use of gastroduodenal or small intestinal protective agents. The manuscript is very well written, very interesting for the readers.

REFERENCES

- Mizukami K, Murakami K, Abe T, Inoue K, Uchida M, Okimoto T, Kodama M, Fujioka T. Aspirin-induced small bowel injuries and the preventive effect of rebamipide. *World J Gastroenterol* 2011; **17**: 5117-5122
- Hiraishi H, Maeda M, Sasai T, Kanke K, Shimada T. [Strategy to manage low dose aspirin-induced gastrointestinal injury]. *Nihon Rinsho* 2011; **69**: 369-375
- García Rodríguez LA, Lin KJ, Hernández-Díaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. *Circulation* 2011; **123**: 1108-1115
- Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011; **9**: 762-768.e6
- Yamamoto T, Isono A, Mishina Y, Ebato T, Shirai T, Nakayama S, Nagasawa K, Abe K, Hattori K, Ishii T, Kuyama Y. Gastroduodenal mucosal injury in patients taking low-dose aspirin and the role of gastric mucoprotective drugs: possible effect of rebamipide. *J Clin Biochem Nutr* 2010; **47**: 27-31
- Ono S, Kato M, Imai A, Yoshida T, Hirota J, Hata T, Takagi K, Kamada G, Ono Y, Nakagawa M, Nakagawa S, Shimizu Y, Takeda H, Asaka M. Preliminary trial of rebamipide for prevention of low-dose aspirin-induced gastric injury in healthy subjects: a randomized, double-blind, placebo-controlled, cross-over study. *J Clin Biochem Nutr* 2009; **45**: 248-253
- Nema H, Kato M. Comparative study of therapeutic effects of PPI and H2RA on ulcers during continuous aspirin therapy. *World J Gastroenterol* 2010; **16**: 5342-5346
- Barozzi N, Tett SE. Gastroprotective drugs in Australia: utilization patterns between 1997 and 2006 in relation to NSAID prescribing. *Clin Ther* 2009; **31**: 849-861
- Watanabe T, Sugimori S, Kameda N, Machida H, Okazaki H, Tanigawa T, Watanabe K, Tominaga K, Fujiwara Y, Oshitani N, Higuchi K, Arakawa T. Small bowel injury by low-dose enteric-coated aspirin and treatment with misoprostol: a pilot study. *Clin Gastroenterol Hepatol* 2008; **6**: 1279-1282
- Fujimori S, Takahashi Y, Seo T, Gudis K, Ehara A, Kobayashi T, Mitsui K, Yonezawa M, Tanaka S, Tatsuguchi A, Sakamoto C. Prevention of traditional NSAID-induced small intestinal injury: recent preliminary studies using capsule endoscopy. *Digestion* 2010; **82**: 167-172
- Nishida U, Kato M, Nishida M, Kamada G, Yoshida T, Ono S, Shimizu Y, Asaka M. Evaluation of small bowel blood flow in healthy subjects receiving low-dose aspirin. *World J Gastroenterol* 2011; **17**: 226-230
- Niwa Y, Nakamura M, Miyahara R, Ohmiya N, Watanabe O, Ando T, Kawashima H, Itoh A, Hirooka Y, Goto H. Geranylgeranylacetone protects against diclofenac-induced gastric and small intestinal mucosal injuries in healthy subjects: a prospective randomized placebo-controlled double-blind cross-over study. *Digestion* 2009; **80**: 260-266
- Iwai T, Ichikawa T, Kida M, Goso Y, Kurihara M, Koizumi W, Ishihara K. Protective effect of geranylgeranylacetone against loxoprofen sodium-induced small intestinal lesions in rats. *Eur J Pharmacol* 2011; **652**: 121-125
- Fang L, Lv B, Meng LN, Zhang S, Wu WF. Preventive effects of different drugs on intestinal damage induced by non-steroidal anti-inflammatory drugs in rats. *Shijie Huaren Xiaohua Zazhi* 2009; **17**: 3244-3248
- Lazzaroni M, Porro GB. Management of NSAID-induced gastrointestinal toxicity: focus on proton pump inhibitors. *Drugs* 2009; **69**: 51-69
- Nakashima S, Ota S, Arai S, Yoshino K, Inao M, Ishikawa K, Nakayama N, Imai Y, Nagoshi S, Mochida S. Usefulness of anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low doses of aspirin. *World J Gastroenterol* 2009; **15**: 727-731
- Fontes-Carvalho R, Albuquerque A, Araújo C, Pimentel-Nunes P, Ribeiro VG. Omeprazole, but not pantoprazole, reduces the antiplatelet effect of clopidogrel: a randomized clinical crossover trial in patients after myocardial infarction evaluating the clopidogrel-PPIs drug interaction. *Eur J Gastroenterol Hepatol* 2011; **23**: 396-404
- Neubauer H, Engelhardt A, Krüger JC, Lask S, Börgel J, Mügge A, Endres HG. Pantoprazole does not influence the antiplatelet effect of clopidogrel—a whole blood aggregometry study after coronary stenting. *J Cardiovasc Pharmacol* 2010; **56**: 91-97
- Kenngott S, Olze R, Kollmer M, Bottheim H, Laner A, Holinski-Feder E, Gross M. Clopidogrel and proton pump inhibitor (PPI) interaction: separate intake and a non-omeprazole PPI the solution? *Eur J Med Res* 2010; **15**: 220-224
- Tunggal P, Ng FH, Lam KF, Chan FK, Lau YK. Effect of esomeprazole versus famotidine on platelet inhibition by clopidogrel: a double-blind, randomized trial. *Am Heart J* 2011; **162**: 870-874
- Murakami M, Oketani K, Fujisaki H, Wakabayashi T, Ohgo T, Okabe S. Effects of the antiulcer drug geranylgeranylacetone on aspirin-induced gastric ulcers in rats. *Jpn J Pharmacol* 1982; **32**: 299-306
- Shiotani A, Haruma K, Nishi R, Fujita M, Kamada T, Honda K, Kusunoki H, Hata J, Graham DY. Randomized, double-blind, pilot study of geranylgeranylacetone versus placebo in patients taking low-dose enteric-coated aspirin. Low-dose aspirin-induced small bowel damage. *Scand J Gastroenterol* 2010; **45**: 292-298
- Sugano K, Matsumoto Y, Itabashi T, Abe S, Sakaki N, Ashida K, Mizokami Y, Chiba T, Matsui S, Kanto T, Shimada K, Uchiyama S, Uemura N, Hiramatsu N. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. *J Gastroenterol* 2011; **46**: 724-735
- El-Abhar HS. Coenzyme Q10: a novel gastroprotective effect via modulation of vascular permeability, prostaglandin E₂, nitric oxide and redox status in indomethacin-induced gastric ulcer model. *Eur J Pharmacol* 2010; **649**: 314-319
- Donnelly MT, Goddard AF, Filipowicz B, Morant SV, Shield MJ, Hawkey CJ. Low-dose misoprostol for the prevention of low-dose aspirin-induced gastroduodenal injury. *Aliment Pharmacol Ther* 2000; **14**: 529-534
- Laine L. Review article: gastrointestinal bleeding with low-dose aspirin - what's the risk? *Aliment Pharmacol Ther* 2006; **24**: 897-908
- Coté GA, Rice JP, Bulsiewicz W, Norvell JP, Christensen K, Bobb A, Postelnick M, Howden CW. Use of physician education and computer alert to improve targeted use of gastroprotection among NSAID users. *Am J Gastroenterol* 2008; **103**: 1097-1103

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