Use of Gastroprotective Drugs in Patients Receiving Low-dose Aspirin

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Background: Low-dose aspirin is widely used for prevention of stroke, heart attacks, and death in patients with atherothrombotic disease, but its use is associated with serious gastrointestinal (GI) adverse effects. Gastroprotective drugs (GPDs) have been used to reduce aspirin-related GI complications but are usually underutilized. The aim of this study was therefore to determine the prescription pattern of GPDs with low-dose aspirin therapy.

Methods: All patients who had attended general and specialist outpatient clinics of Tung Wah Hospital between September 1, 2007 and September 30, 2007 and received low-dose aspirin therapy were included in the study. Data were collected through retrospective chart review and recorded on a standardized data collection form. Univariate analysis was performed using χ^2 tests for discrete variables. Factors that might be associated with prescription of GPD with low-dose aspirin were assessed in multiple logistic regression models.

Results: Three hundred and three patients were included in this study, and the rate of GPD prescription was 48.5%. Most of the patients received H_2-receptor antagonist, and, to a lesser degree, antacid and proton pump inhibitor. Patients with history of GI ulcer/bleeding were much more likely to be co-prescribed GPD than those who had no history of GI disorders (OR, 26.5). Compared with patients who were managed in general outpatient clinic, those managed in specialist clinic were more likely to receive GPD (OR, 3.04).

Conclusion: The prescription rate of GPD with aspirin is low. Also, it seems that physicians are unaware of the risk factors related to aspirin-induced GI complications. [*J Chin Med Assoc* 2009;72(7):356–361]

Key Words: anti-ulcer agents, aspirin, drug utilization

Introduction

Low-dose aspirin is widely used for prevention of stroke, heart attacks, and death in patients with atherothrombotic disease. In a survey conducted by Wood et al, it was found that among 29.3% of patients who were suffering from ≥ 1 macrovascular complications (ischemic heart disease, cerebrovascular disease or peripheral vascular disease), 63% were on aspirin treatment.[1] A meta-analysis which included the European Stroke Prevention Study 2 trial found an overall 13% risk reduction in vascular morbidity and mortality among patients receiving aspirin therapy.[2] In another meta-analysis of low-dose aspirin for secondary cardiovascular prevention, aspirin reduced both the reinfarction and mortality rates.[3] The American Heart Association has extended the indications for aspirin to the primary prevention of cardiovascular events in anyone with a calculated 10-year cardiovascular risk of ≥ 10%.[4] However, the use of aspirin is associated with potentially serious gastrointestinal (GI) adverse effects. It has been estimated that low-dose aspirin prevents 2–3 recurrent strokes at the expense of 1 extra episode of GI bleeding per year.[3,5] With the increasing use of aspirin for cardiovascular protection, the incidence of GI complications can be expected to increase in the near future. Various strategies have been used to reduce aspirin-related GI injury. One approach is to co-administer gastroprotective drugs (GPDs) with aspirin. The most common classes of gastroprotective agent used in our hospital were antacids and H_2-receptor antagonists.[6] The use of antacids and H_2-receptor antagonists as GPDs is probably not confined to our hospital alone but appears to be widespread among other hospitals.[7–9]

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This practice, however, is not consistent with existing evidence, as only misoprostol and proton pump inhibitor (PPI) have been proven to reduce the incidence of nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers.[10–13] Antacids may afford some symptomatic relief, but offers no protection against aspirin-induced GI complications.[7–9] Due to the problems related to the utilization of GPDs with low-dose aspirin, the prescription pattern of gastroprotective medications associated with low-dose aspirin therapy needs to be evaluated. The aim of this study was therefore to determine the prescription pattern of GPDs with low-dose aspirin therapy.

Methods

This retrospective study was conducted at Tung Wah Hospital, Hong Kong. This is one of the major hospitals in western Hong Kong, and serves a population of about 0.6 million. A computerized search of dispensing records was used to identify patients who had attended general and specialist outpatient clinics of Tung Wah Hospital between September 1, 2007 and September 30, 2007. The medical records of recruited patients were obtained from the Medical Records Department for further investigation. Patients were included in the analysis if they were over the age of 18 and had received low-dose aspirin (< 300 mg daily) for a minimum of 3 months. Patients with incomplete medical record or who had used aspirin externally (gargle) were excluded from the study.

Data were collected through retrospective chart review by the investigator, and recorded on a standardized data collection form. Continuous and categorical data were expressed as mean and counts, respectively. Univariate analysis was performed using χ^2 tests for discrete variables. A difference with a p value < 0.05 was considered significant. A multiple logistic regression model was developed to identify factors that might be associated with prescription of GPDs with low-dose aspirin. The adequacy of model fit was assessed by Hosmer-Lemeshow χ^2 tests. All data were analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows. This study was approved by the institutional review board of the University of Hong Kong.

On the data collection form, GI risk factors were defined as: (1) age ≥ 65 years; (2) previous clinical history of gastroduodenal ulcer, GI bleeding or gastroduodenal perforation; (3) concomitant use of medications that are known to increase upper GI adverse events, e.g. corticosteroids and anticoagulants; (4) presence of serious comorbidity such as cardiovascular disease, renal or hepatic impairment, diabetes and hypertension.[14]

Results

During the period September 1 to September 30, 2007, 311 patients presented prescriptions for aspirin to the pharmacy, of which 303 patients were included in the study. Of the 8 patients who were excluded from the study, 4 had incomplete medical records, 2 used aspirin for duration < 2 weeks, and 2 used aspirin externally as gargles. The main characteristics of the patients are summarized in Table 1. Patient age ranged from 37 to 95 years, with a mean ± standard deviation of 72 ± 10 years. Female subjects were slightly older than male patients (74.2 years *vs.* 70.0 years, $p < 0.001$). No sex difference was observed for the concomitant medications, GPD co-prescription rate, and clinical settings. More female patients presented with concomitant diabetes mellitus than male patients (52.6% *vs.* 31.5%, $p < 0.001$). Compared with female patients, more male subjects had previous history of peptic ulcer/GI bleeding (17.9% *vs.* 4.4%, $p < 0.001$). No differences were found among other concomitant diseases between female and male patients. All of the 303 patients had ≥ 1 GI risk factors, which identified them as patients at high risk of developing aspirin-associated complications, and most of them (81.5%) had ≥ 2 GI risk factors. The rate of GPD prescription was 48.5%. Most of the patients received H_2-receptor antagonist, and, to a lesser degree, antacid and PPI.

Univariate analysis

Factors that might be associated with the decision to co-prescribe aspirin and GPD were separated into 3 groups: those related to patients' demographic characteristics, those related to patients' clinical conditions, and those related to clinical setting. Results of the univariate analysis are shown in Table 1. The mean ages of patients with and without GPD co-prescription were 72.5 and 71.2 years, respectively. Previous history of gastroduodenal ulcer/bleeding, renal impairment and hypercholesterolemia, presence of GI risk factor, and clinical setting were significant determinants of GPD co-prescription. Patients with documented prior history of GI diseases were more likely to receive GPDs (23.8%), whereas those without GI problems were less likely to (0.6%). In patients with renal impairment, 15% were co-prescribed GPDs compared with 6.4% of patients with normal renal function. Patients managed in specialist clinics were associated with a high prescription rate of GPDs.

Table 1. Demographic characteristics and univariate analysis*

	With gastroprotection ($n=147$)	No gastroprotection ($n=156$)	p
Age group (yr)			
<45	1 (0.7)	2 (1.3)	
45–64	30 (20.4)	31 (19.9)	
≥65	116 (78.9)	123 (78.8)	0.87
Sex			
Male	87 (59.2)	81 (51.9)	0.20
Smoking habits			
Smoker	24 (16.3)	22 (14.1)	
Non-smoker	115 (78.2)	117 (75.0)	
Unknown	8 (5.5)	17 (10.9)	0.21
Drinking habits			
Drinker	13 (8.8)	12 (7.7)	
Non-drinker	122 (83.0)	121 (77.6)	
Unknown	12 (8.2)	23 (14.7)	0.20
Concomitant diseases			
Hypertension	126 (85.7)	147 (92.9)	0.06
Hypercholesterolemia	51 (34.7)	73 (46.8)	0.04
Diabetes mellitus	57 (38.8)	67 (42.9)	0.46
Osteoarthritis	5 (3.4)	4 (2.6)	0.67
History of GD ulcer/bleeding	35 (23.8)	1 (0.6)	<0.001
Renal impairment	22 (15.0)	10 (6.4)	0.02
GI risk factors (n)			
1	23 (15.6)	33 (21.2)	
2	94 (63.9)	21 (77.6)	
3	30 (20.5)	2 (1.2)	<0.001
Concomitant medications			
Antiplatelet	2 (1.4)	2 (1.3)	0.30
Anticoagulant	1 (0.7)	0 (0)	0.95
Gastroprotective drug prescription	147 (96.6)	138 (88.5)	0.01
Clinical setting			
Specialist clinic	142 (96.6)	138 (88.5)	0.01

**Data presented as n (%). GD = gastroduodenal; GI = gastrointestinal.*

Patients with >2 risk factors were more likely to be co-prescribed a GPD.

Multivariate analysis

In the multivariate analysis (Table 2), only previous history of gastroduodenal ulcer/bleeding and clinical setting were significant determinants of GPD co-prescription (Hosmer-Lemeshow χ^2, 3.37; degrees of freedom, 6; $p=0.761$). After adjustment, hypercholesterolemia, renal impairment, and GI risk factors were no longer predictors of GPD use. As expected, previous history of gastroduodenal ulcer/bleeding significantly influenced the use of GPD. Patients with history of GI ulcer/bleeding were much more likely to be co-prescribed a GPD than those who had no history of GI disorders (OR, 26.5). Compared with patients who were managed in general outpatient clinic, those managed in specialist clinic were more likely to receive GPD (OR, 3.04).

Discussion

The aim of the present study was to determine the prevalence of concomitant use of GPD with low-dose aspirin and the potential factors associated with co-prescription.

Risk factors for GI complications were very common among aspirin users in the present study. Overall, all patients had at least 1 risk factor, and 81.5% had ≥2 risk factors. Such an observation is consistent with the results of the study of Targownik and Al-Mamfud.[15] They reported that 78% of aspirin users had at least

Table 2. Multivariate analysis of determinants of gastroprotective drugs co-prescription

	Odds ratio	95% confidence interval	*p*
Hypertension	0.489	0.214–1.109	0.087
Hypercholesterolemia	0.703	0.422–1.173	0.177
Previous history of GI ulcer/bleeding	26.493	2.565–273.60	0.006
Renal impairment	2.21	0.960–5.094	0.062
Clinical setting	3.04	1.001–9.206	0.049
GI risk factors (*n*)			
1	1		
2	1.105	0.595–2.051	0.752
3	2.493	0.357–17.399	0.357

GI = gastrointestinal.

1 risk, in addition to cardiovascular disease, and 15% had ≥ 3 risk factors.

Despite high prevalence of GI risk factors, the prescription rate of GPDs among aspirin users was low in this study. Overall, 48.5% of patients received concomitant GPD, and the prescription rate of GPD among patients with a history of gastroduodenal ulcer/bleeding or with ≥ 2 risk factors for GI complications was 50.2%. The American College of Rheumatology guidelines recommend that patients with at least 1 GI risk factor should receive either an NSAID plus a co-prescribed protective agent or a COX-2 inhibitor,[16] as do the NICE (National Institute for Clinical Excellence) guidelines.[14] However, these guidelines apply to NSAID for treatment of rheumatoid arthritis or osteoarthritis. Although aspirin is considered to be an NSAID, the absolute risk of GI complications for low-dose aspirin users is likely to be lower than that for NSAID users. Targownik and Al-Mamfud recommend that GPDs should be used in aspirin users with a history of gastroduodenal ulcer/bleeding, or in patients with ≥ 2 risk factors for GI complications, of which 1 of the risk factors may be established cardiovascular disease.[15] Therefore, the percentage of appropriate treatment, 50.2%, was in accordance with Targownik and Al-Mamfud's recommendation. The prescription rate of GPDs in this study is relatively higher when compared to similar studies by other investigators. In the study by Targownik and Al-Mamfud, it was found that only 24% of aspirin users were discharged on appropriate GPDs.[15] A Dutch study reported that only 14% of elderly patients taking NSAIDs were prophylactically prescribed an H_2-receptor antagonist, PPI or misoprostol.[17] In a national veterans affairs survey, 27.2% of patients received therapy appropriate to GI risk factors.[18] More recently, a U.S. study demonstrated that among patients at risk for NSAID-induced GI adverse events, only 26% were receiving prophylactic treatment.[19] Taken together, these results indicate that the majority of patients treated with aspirin/NSAIDs who would benefit from protective therapies are not being appropriately treated.

The problem of underutilization of GPDs is not unique to Hong Kong but also occurs in North America and Europe and may be due to several reasons.[20–22]

Firstly, there may be a belief that low-dose aspirin is safe and can be used for high-risk patients without protective measures. However, aspirin is able to inhibit prostaglandin synthesis even at doses as low as 10 mg/day.[23] In a meta-analysis by Derry and Loke, the pooled odds ratio for bleeding with aspirin was 1.68.[5] More recently, a meta-analysis of 14 trials showed that the relative risk of major GI bleeding with the use of low-dose aspirin as compared with placebo was 2.07.[24] A large 5-year observational cohort study from Denmark also showed that the annual incidence of hospitalization for upper GI bleeding was 0.60% for low-dose aspirin users.[25] In summary, meta-analyses as well as observational studies indicate that low-dose aspirin approximately doubles the risk of major GI bleeding and is actually not as safe as expected.

Secondly, since the aspirin used in our hospital is enteric-coated, there may be a misbelief that this formulation is relatively safe. In a survey by Chey et al of perceptions of primary care physicians regarding aspirin-associated toxicity, it was found that more than half (53%) thought enteric-coated or buffered aspirin reduced the risk of upper GI bleeding.[26] However, current evidence suggests that enteric-coating or buffering of aspirin does not reduce the risk of upper GI bleeding.[27]

Thirdly, numerous guidelines on the proper use of gastroprotective strategies for chronic NSAID users have been published, but there are no similar guidelines for low-dose aspirin users.[14,16] The lack of official guidelines may lead to the underutilization of GPDs among low-dose aspirin users. Although the absolute risk of GI

complications for low-dose aspirin is likely to be lower than for NSAID users, low-dose aspirin is still associated with serious GI complications.[15,24,25,28] Therefore, it is not justified to provide no protective strategies for a patient who is at risk of aspirin-related complications.

Fourthly, the benefits of GPDs in low-dose aspirin users may be underappreciated, as there have been few trials where gastroprotection strategies have been used with low-dose aspirin.[15] However, the efficacy of GPDs in low-dose aspirin users has recently been proven in 2 Hong Kong studies. They showed that PPIs effectively reduce aspirin-associated GI adverse events.[29,30]

Lastly, there may be a lack of knowledge about risk factors related to aspirin-induced GI toxicity. It is possible that physicians have insufficient knowledge about different risk factors and thus do not routinely evaluate whether aspirin users are at risk for developing aspirin-associated GI adverse events. This is supported by our findings as well as Erdeljic et al's, which demonstrated that the number of risk factors did not increase the odds of GPD prescriptions in the multivariate analysis.[31]

Although the co-prescription rate of GPDs in the present study was relatively high compared to that in similar studies, when recommended classes of GPDs were taken into consideration, the actual prevalence of gastroprotection was unacceptably low (6.3%). H_2-receptor antagonists was the most used (64.6%) and, to a lesser degree, antacids (22.4%) and PPIs (13.0%), and no patients received prostaglandin analog. Obviously, the pattern of GPD use was not consistent with current evidence. Currently, 4 classes of drugs, namely PPI, prostaglandin analog, H_2-receptor antagonist and antacid, are available for co-therapy with NSAID, but only PPI and prostaglandin analog have been shown to be effective at preventing NSAID-associated gastric and duodenal ulcers.[10–13] Furthermore, only misoprostol at a dose of 800 μg/day has been demonstrated to reduce the risk of ulcer complications.[32] There is evidence from randomized controlled trials that double-dose H_2-receptor antagonist (e.g. famotidine 40 mg twice daily, or ranitidine 300 mg twice daily) reduces the incidence of both endoscopic duodenal and gastric ulcers compared with placebo.[33,34] However, there is no clinical outcome study to show whether high doses prevent ulcer complications. Taken together, the available data show that of all the possible GPDs, only 2 classes are acceptable: PPI and prostaglandin analog. The use of double-dose H_2-receptor antagonist is controversial and thus not recommended. Standard-dose H_2-receptor antagonist and antacid are not considered appropriate treatment in NSAID-induced ulcer prophylaxis. These drugs may provide patients with a false sense of security when they are still exposed to a real risk. In fact, antacid and H_2-receptor antagonist can double the risk of serious GI events by dangerously masking symptoms of GI irritation.[7,35,36] Interestingly, no patients in our study received misoprostol, and this result is comparable to those of studies conducted in Europe.[37] The reason for this is probably related to its unfavorable tolerability profile and inconvenient dosing schedule.[32] So, our study revealed a lack of knowledge among physicians about the details of preventive strategies, especially with regard to efficacy and appropriate regimens.

In multivariate analysis, a variety of factors that significantly influenced the use of GPDs were identified. Among the various risk factors for upper gastroduodenal damage in patients receiving low-dose aspirin therapy, only previous history of gastroduodenal ulcer/bleeding was identified as a significant factor associated with the co-prescription of GPDs. Patients with history of gastroduodenal ulcer/bleeding were much more likely to be co-prescribed a GPD. These results indicate that physicians were aware of previous history of gastroduodenal ulcer/bleeding as a risk factor for aspirin-related GI adverse events but had insufficient knowledge about other risk factors related to increased risk.

Clinical setting was another significant determinant of GPD co-prescription. Patients treated at specialist clinics had a greater likelihood of receiving a GPD (OR, 3.04) than those treated at general outpatient clinics. This is probably due to pharmacy formulary restriction in which PPI is not available in general outpatient clinic formulary. It could also be possible that the most severe patients, as would be expected, were managed in specialist clinics.

There are some limitations to our study. This was a retrospective study, and data were collected through chart review. The accuracy and completeness of data collection depended on documentation by physicians. Incomplete or poor documentation might have caused incorrect or missing data in the medical records, thus resulting in inaccurate data collection.

In conclusion, the prescription pattern of GPDs in low-dose aspirin users was not consistent with literature recommendations, and this indicates the need for further educational measures.

References

1. Wood DM, Plehwet WE, Colmant PG. Aspirin usage in a large teaching hospital diabetes clinic setting. *Diabet Med* 1999; 16:605–8.

2. Albers GW, Tijssen JG. Antiplatelet therapy: new foundations for optimal treatment decisions. *Neurology* 1999;53:S25–31.
3. Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med* 2002;162: 2197–202.
4. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklinet BA, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke, 2002 update. Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002;106:388–91.
5. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000;321: 1183–7.
6. Luk HH, Pang J, Li LSW, Ng M. Use of antiplatelet drugs in the stroke unit of a Hong Kong hospital. *Pharm World Sci* 2005;27:258–62.
7. See Y, Ng SC, Tho KS, Teo SK. Are antacids necessary as routine prescriptives with non-steroidal anti-inflammatory drugs? *Ann Acad Med Singap* 1998;27:219–22.
8. Lim KH, Yap KB. The prescribing pattern of outpatient polyclinic doctors. *Singapore Med J* 1999;40:416–9.
9. Yap KB, Chan KM. The prescribing pattern of hospital doctors. *Singapore Med J* 1998;39:496–500.
10. Chan FKL. Management of high-risk patient on nonsteroidal anti-inflammatory drugs or aspirin. *Drugs* 2006; 66(Suppl):23–8.
11. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340:1888–99.
12. Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:25–8S.
13. Chan FKL, Leung WK. Peptic-ulcer disease. *Lancet* 2002;360: 933–40.
14. National Institute for Clinical Excellence. Guidance on the use of cyclooxygenase (COX) II selective inhibitors celecoxib, rofecoxib, meloxicam and todolac for osteoarthritis and rheumatoid arthritis. *Technology Appraisal Guidance No. 27.* Available at http://guidance.nice.org.uk/TA27/guidance/pdf/English [Date accessed: December 1, 2007]
15. Targownik LE, Al-Mamfud A. The prevalence of risk factors for gastrointestinal complications and use of gastroprotection among persons hospitalized for cardiovascular disease. *Aliment Pharmacol Ther* 2006;23:743–9.
16. American College of Rheumatology. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002;46:328–46.
17. van Dijk KN, ter Huurne K, de Vries CS, van den Berg PB, Brouwers JR, de Jong-van den Berg LT. Prescribing of gastroprotective drugs among elderly NSAID users in The Netherlands. *Pharm World Sci* 2002;24:100–3.
18. Abraham NS, El-Serag HB, Johnson ML, Hartman C, Richardson P, Ray WA, Smalley W. National adherence to evidence-based guidelines for the prescription of nonsteroidal anti-inflammatory drugs. *Gastroenterology* 2005;129:1171–8.
19. Harris CL, Raisch DW, Abhyankar U, Marfatia S, Campbell HM, Sather MR. GI risk factors and use of protective agents among patients receiving nonsteroidal antiinflammatory drugs. *Ann Pharmacother* 2006;40:1924–31.
20. Hogan DB, Campbell NR, Crutcher R, Jennett P, MacLeod N. Prescription of nonsteroidal anti-inflammatory drugs for elderly people in Alberta. *CMAJ* 1994;151:315–22.
21. Clinard F, Bardou M, Sgro C, Lefevre N, Raphael F, Paille F, Dumas M, et al. Non-steroidal anti-inflammatory and cytoprotective drug co-prescription in general practice: a general practitioner-based survey in France. *Eur J Clin Pharmacol* 2001;57:737–43.
22. Caputi AP, Kong SX, Mavros P, Ricci E, Russo A. Concomitant use of gastroprotective agents among users of nonsteroidal antiinflammatory drugs in Italy. *Ann Rheum Dis* 2001; 60(Suppl):275.
23. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999;117:17–25.
24. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006;119:624–38.
25. Sorensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, Olsen JH. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000;95:2218–24.
26. Chey WD, Eswaren S, Howden CW, Inadomi JM, Fendrick AM, Scheiman JM. Primary care physician perceptions of nonsteroidal anti-inflammatory drug and aspirin-associated toxicity: results of a national survey. *Aliment Pharmacol Ther* 2006;23: 655–68.
27. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996; 348:1413–6.
28. Ibanez L, Vidal X, Vendrell L, Moretti U, Laporte JR. Upper gastrointestinal bleeding associated with antiplatelet drugs. *Aliment Pharmacol Ther* 2006;23:235–42.
29. Lai KC, Lam SK, Chu KM, Wong BC, Hui WM, Hu WH, Lau KK, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033–8.
30. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, Hui AJ, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005; 352:238–44.
31. Erdeljic V, Francetic I, Sarinic VM, Bilusic M, Auaperger KM, Huic M, Mercep I. Use of gastroprotective agents in recommended doses in hospitalized patients receiving NSAIDs: a drug utilization study. *Pharm World Sci* 2006;28:318–25.
32. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, Geis GS. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; 123:241–9.
33. Ong CKS, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res* 2007;5:19–34.
34. Micklewright R, Lane S, Linley W, McQuade C, Thompson F, Maskrey N. NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors. *Aliment Pharmacol Ther* 2003;17: 321–32.
35. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. *Arch Intern Med* 1996;156:1530–6.
36. Lazzaroni M, Sainaghi M, Bianchi PG. Non-steroidal anti-inflammatory drug gastropathy: clinical results with antacids and sucralfate. *Ital J Gastroenterol Hepatol* 1999;31:S48–53.
37. Lanas A, Ferrandez A. Inappropriate prevention of NSAID-induced gastrointestinal events among long-term users in the elderly. *Drugs Aging* 2007;24:121–31.