Aspirin and gastrointestinal toxicity

Aspirinin gastrointestinal yan etkileri

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ABSTRACT

Aspirin is the main actor in primary and secondary preventive treatments in cardiovascular diseases. However, it has several side effects including gastrointestinal toxicity (peptic ulcer formation, bleeding). Although lower doses are relatively safe, we should keep in mind that even the lowest dose may cause gastrointestinal bleeding. Gastrointestinal toxicity profile does not differ between conventional and enteric-coated aspirin use. In patients who have cardiovascular disease but are at high risk for gastrointestinal bleeding, eradication of Helicobacter pylori infection and concurrent proton pump inhibitor therapy may help to reduce the risk of gastrointestinal toxicity. *(Anadolu Kardiyol Derg 2007; 7 Suppl 2; 27-30)*

Key words: Aspirin, gastrointestinal system, toxicity

ÖZET

Aspirin kardiyovasküler hastalıklardan primer ve sekonder korunmada temel tedavilerden birisidir. Ancak bu faydalı etkilerinin yanında ciddi gastrointestinal yan etkilere neden olabilmektedir. Düşük doz kullanımı göreceli olarak gastrointestinal yan etki insidansını azaltıyor görünse de kullanılan en düşük dozlarda bile gastrointestinal yan etkilerle (peptik ülser, gastrointestinal sistem kanamaları) karşılaşılabileceği unutulmamalıdır. Yapılan çalışmalar enterik kaplı aspirin ile konvansiyonel aspirin arasında gastrointestinal toksisite profili açısından belirgin bir fark olmadığını düşündürmektedir. Gastrointestinal kanama riski yüksek olup da aspirin kullanması gereken hastalarda en akılcı strateji (varsa) Helicobacter pylori enfeksiyonunun eradike edilmesi ve tedaviye proton pompa inhibitörlerinin eklenmesi olarak görünmektedir. *(Anadolu Kardiyol Derg 2007; 7 Özel Sayı 2; 27-30)*

Anahtar kelimeler: Aspirin, gastrointestinal sistem, yan etki

Introduction

Cardiovascular disease (CVD), including stroke and coronary artery disease, is the leading cause of death in developed countries. Evidence based research including randomized controlled trials and observational studies have shown beneficial effects of aspirin in decreasing the risk of CVD in majority of patients. However, despite its protective effect in CVD, aspirin has gastrointestinal side effects. In this article, gastrointestinal toxicity of aspirin and possible prevention strategies from this toxicity will be reviewed.

Aspirin inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) but is a more potent inhibitor of COX-2 (1). Irreversible acetylation of COX-1 by aspirin inhibits formation of prostaglandins and thromboxane A2 from arachidonic acid which results in preventing platelet aggregation and thrombi formation (1). Following Paul Gibson's proposal suggesting that salicylic acid might be used in CVD (2), aspirin use in CVD became prevalent in subsequent years. Aspirin use was primarily for conditions like inflammation, fever and pain. However, its ability of irreversible inhibition of platelet thromboxane synthesis led to its long-term use especially in CVD. Nowadays, it is the main part of the treatment. Nevertheless, aspirin use can cause some side effects including gastrointestinal toxicity, which causes the major limitation of its use in CVD. First observation related to the gastrointestinal damage caused by aspirin was reported in 1938 depending on endoscopic observations (3). Gastrointestinal side effects of aspirin include nausea, vomiting, dyspepsia, heartburn, gastrointestinal ulceration, duodenal ulcers and perforations due to the ulcers. Dyspepsia might occur in 25-50% of the patients while symptomatic gastroduodenal ulcer and incidence was reported in 4-8% of the patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (4). These gastrointestinal side effects are due to decreased levels of prostaglandin E2 and prostaglandin I2 and irreversible inhibition of thromboxane (5). Another effect is likely to be the direct effect on gastric mucosa. Interestingly, effect on platelets is dose independent whereas, effects on prostaglandin synthesis and gastric mucosa are dose dependent (6).

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Anatol J Cardiol 2007: 7 Suppl 2; 27-30
Anadolu Kardiyol Derg 2007: 7 Özel Sayı 2; 27-30

Relation of aspirin dose with gastrointestinal toxicity

In a study evaluating short-term pharmacodynamics of ingested aspirin, authors have shown that acute antiplatelet activity of 300 mg/d and 500mg/d doses were superior to 40 mg/d and 100 mg/d doses. However, there was no additional benefit over 300 mg/d dosing regimen (7). A meta-analysis of nearly 60 aspirin trials found no correlation between aspirin dose and its clinical efficacy, however efficacy of 75 mg/d to 150 mg/d doses were slightly superior than others (8). Pharmaceutical market research have shown that, the dose of aspirin preferred by physicians is in favor of 81 mg/d (60%) whereas 30% of physicians prefer prescribing 325 mg/d. Interestingly, in a subgroup of cardiologists frequency of 325 mg/d prescriptions is slightly over 81 mg/d (9).

UK transient ischemic attack (TIA) trial, evaluated 2435 patients who had TIA previously. The patients were randomized to take aspirin 300 mg/d, 1200 mg/d and placebo. This study showed a dose dependent increase in gastrointestinal bleeding, odds ratio (OR) - 3.3 (95% CI1.2-9.0) for 300 mg/d and OR - 8.7 (95% CI 2.5-16.5) for 1200 mg/d. Besides, hospitalization ratio was higher in 1200 mg/d group than in 300 mg/d group (OR - 3.6 [95% CI 0.7-17.2] vs. OR - 8.7 [95% CI2.0-37.6]) (10). In another study, which compared the doses of 30 mg/d and 283 mg/d aspirin for patients with TIA, major bleeding episodes were slightly more common in 283 mg/d group than in 30 mg/d group (3.4% vs 2.6%). Minor bleeding episodes were also more common in 283 mg/d users (5.3% vs 3.2%). Overall, gastrointestinal symptoms were reported to some extent lower in 30 mg/d group than in 283 mg/d (10.5% vs. 11.4%) (11).

A recent meta-analysis of 31 clinical trials with more than 192 000 patients has shown that, aspirin therapy with doses of less than 100 mg/d caused significantly lower major bleeding rate than doses of greater than 200 mg/d (1.56% [95% CI, 1.2%-1.9%] vs. 2.29% [95% CI, 1.9%-7.0%], p<0.001) (12). However, not all the studies have agreed that gastrointestinal bleeding is directly related with aspirin dose. In another meta-analysis involving 24 trials with nearly 66 000 participants, no association was found between aspirin dose and gastrointestinal bleeding. In this study, a meta-regression was performed to test for a linear relation between daily dose of aspirin and the risk of gastrointestinal bleeding. This analysis gave a pooled odds ratio of 1.015 (95%CI - 0.984 to 1.047) per 100 mg dose reduction, with an estimated relative reduction in the incidence of gastrointestinal bleeding of 1.5% per 100 mg reduction of dose, but this reduction was not significant (p=0.3) (13). Gastrointestinal bleeding was increased by approximately two times and the absolute excess risk of aspirin was 4:1000 patients receiving aspirin per one year (13). Ridker et al. (14), have reported that low dose aspirin (100 mg) even in alternating day use increases the risk of peptic ulcer formation (relative risk (RR) - 1.32 [95% CI, 1.16-1.1.5], p<0.001) and gastrointestinal bleeding over placebo group (RR - 1.22 [95% CI, 1.1-1.34], p<0.001) .

In summary, although it is well established that any dose of aspirin use increases the risk of gastrointestinal bleeding, it is still controversial whether using lower doses of aspirin results with less damage to gastroduodenal mucosa. It should be noted that, using lower dose or even alternating treatment schedules does still cause gastrointestinal mucosal damage to some extent.

Relation of aspirin formulation with gastrointestinal toxicity

Since lowering or alternating the dose of aspirin did not decrease the risk of peptic ulcer formation and gastrointestinal bleeding, different formulations of aspirin to reach to an acceptable adverse-effect profile have been investigated. To eliminate the direct effect of aspirin to gastric mucosa, coating of aspirin has been proposed as an approach.

Dammann et al. (15), have reported a lesser gastrointestinal mucosal injury with enteric coated low-dose aspirin (100 mg/d) when compared to plain aspirin and placebo over a limited time of use (7 or 15 days). The mean gastrointestinal mucosal damage scores were significantly lower in enteric coated aspirin group on day 1 and 7 than in plain aspirin group (3.95 ± 3.38 vs. 6.53 ± 4.1 and 1.43 ± 1.91 vs 2.00 ± 2.02, p=0.03 and p=0.002, respectively). In another study, comparing the acute gastrointestinal toxicity of plain and enteric coated aspirin, Cole et al. (16), found that gastrointestinal mucosal damage by enteric coated aspirin was not different from placebo. By 5 days treatment with 300 mg enteric coated aspirin there were 0 (0-1) gastric erosions while there were 2 (0-7) and 18 (2-26) gastric erosions in 75 mg and 300 mg plain aspirin group (p>0.05 and p=0.003, respectively) (16).

Despite the safer profile of enteric coated aspirin in short term use, recent publications showed that it does not reduce the risk of gastrointestinal mucosal damage in long term use. Sorensen HT et al. (17), compared the incidence of upper gastrointestinal system bleeding in 27 694 low dose aspirin users with the incidence of general population over 4 years. They found that the risk was similar among users of non-coated low-dose aspirin (standardized incidence rate ratio, 2.6; 95% CI, 1.8 -3.5) and coated low-dose aspirin (standardized incidence rate ratio, 2.6; 95%CI, 2.2-3.0). In a case control study evaluating the effect of aspirin on gastrointestinal bleeding, RR for gastrointestinal bleeding in aspirin users (75-300 mg) was found as 2.0 (95% CI - 1.7-2.3). The RR associated with enteric-coated formulations (2.3, 95% CI - 1.6-3.2) was similar to that of plain aspirin (1.9, 95% CI 1.6-2.3) (18).

Another formulation of aspirin that has been studied is nitric oxide donating aspirin (NO-aspirin). Pre-clinical studies showed that NO-aspirin has reduced gastrointestinal side-effects of aspirin while retaining antiinflammatory, antithrombotic and analgesic effects (19-21). A double-blind, placebo-controlled pilot study assessing the effect of NO-aspirin and aspirin on gastrointestinal mucosa and platelet aggregation in healthy human volunteers has shown that NO-aspirin reduced the gastrointestinal toxicity almost to placebo levels. In that study, 5 groups of healthy volunteers received either placebo, aspirin 200 mg, aspirin 420 mg, NO-aspirin 400 mg or NO-aspirin 800 mg for 7 days. Then, upper gastrointestinal endoscopy was performed to assess mucosal damage. Mean total endoscopic score was 11.0 ± 3.0 and 16.1 ± 1.6, respectively in aspirin 200 mg and 400 mg groups (p<0.0001 vs. placebo) while mean total endoscopic score was 1.38 ± 0.5 and 1.25 ± 0.3, respectively in NO-aspirin 400 mg and NO-aspirin 800 mg groups (p<0.0001 vs. plain aspirin groups) (22).

However, further studies are needed to explore NO-aspirin's effect on gastrointestinal toxicity in long-term use and to define its clinical benefits in CVD.

Which patients are at increased risk for gastrointestinal toxicity?

Since NSAIDs, including aspirin, cause considerable morbidity and mortality related to gastric and duodenal ulcer disease, risk factors for gastrointestinal toxicity should be evaluated cautiously. A committee appointed by the American College of Gastroenterology identified the five most important risk factors (23);

- Prior history of peptic ulcer or hemorrhage
- Age > 60
- Higher dosage of NSAID
- Concurrent use of corticosteroids
- Concurrent use of anticoagulants

Serrano et al., (24) evaluated the risk factors affecting upper gastrointestinal bleeding in low-dose aspirin users. In this study, they reported that relative risk for hospitalization due to gastrointestinal bleeding was 3.1 (95% CI - 1.5-6.5, p=0.003) in patients with prior history of peptic ulcer or upper gastrointestinal system bleeding. Age, sex and concurrent non-aspirin NSAID use did not increase the risk of gastrointestinal bleeding in multivariate analysis.. In contrast, there are some other studies showing that, the risk of ulcer bleeding in patients taking combination of NSAIDs and aspirin is approximately two fold greater than (OR 7.7; 95% CI 3.6-16.4) that of patients who take either NSAIDs (OR 4.9; 95% CI 3.9-6.1) or aspirin alone (OR 3.3; 95% CI 2.5-4.4) (25). Older age is another risk factor associated with gastrointestinal bleeding in low-dose aspirin users (26). Another factor, which is believed to increase the risk of upper gastrointestinal toxicity due to aspirin use, is Helicobacter Pylori (H. pylori) infection. However, reports are controversial. There are data to suggest that H. pylori increases (27), or has no effect (28), or even decreases (29) the risk of bleeding among users of aspirin or other NSAIDs. On the other hand, eradicating H. pylori decreases the risk of gastrointestinal bleeding in low-dose aspirin users (30). A recent meta-analysis (21) reviewing 21 studies involving 10 146 patients has shown that, peptic ulcer was more prevalent among H. pylori - positive than H. pylori - negative patients irrespective of NSAID use (OR, 4.03) and more prevalent among NSAID users than non-users irrespective of H. pylori status (OR, 3.10). The risk of ulcer was 17.54-fold higher in H. pylori - positive NSAID users than H. pylori - negative non-users. The use of aspirin or non-aspirin NSAIDs did not affect the results (31). On the basis of these data, it seems reasonable to eradicate H. pylori in patients with high risk of gastrointestinal bleeding (older age, concomitant NSAID or steroid use, history of previous ulcer history). There are no valid data supporting H. pylori eradication in long-term low dose aspirin users with low risk of gastrointestinal bleeding (32).

As antithrombotic treatment is becoming more aggressive, the risk of gastrointestinal bleeding in patients receiving combination of antithrombotics such as aspirin plus clopidogrel is questioned. Hallas J et al. (33), assessed the risk of serious upper gastrointestinal bleeding associated with the newer antithrombotic agents used alone or in combination with other antithrombotic drugs. In this case-controlled study, they found that adjusted odds ratios for combined use were 7.4 (95% CI - 3.5 to 15) for clopidogrel and aspirin, 5.3 (95% CI - 2.9 to 9.5) for vitamin K antagonists and aspirin, and 2.3 (95% CI - 1.7 to 3.3) for dipyridamole and aspirin, while for low dose aspirin alone odds ratio was 1.8 (95% CI - 1.5 to 2.1) (33).

Treatment options for aspirin users with high risk of gastrointestinal bleeding

Despite its well-known gastrointestinal toxicity, low dose aspirin is the corner stone in primary and secondary prevention against CVD. Therefore, strategies against its gastrointestinal toxicity have been searched intensively. A meta-analysis of 33 randomized controlled trials showed that high dose misoprostol, double dose H2 receptor blockers and proton pump inhibitors (PPIs) had a preventive effect against NSAIDs' (including aspirin) gastrointestinal toxicity (34). A case-controlled study evaluating 2777 patients with upper gastrointestinal system bleeding showed that, PPIs and H2 receptor blockers both reduced the risk of gastrointestinal bleeding in patients receiving NSAIDs including aspirin. However, PPI use was associated with greater reductions among low-dose aspirin users (RR 0.32, 95% CI 0.22-0.51 vs RR 0.40, 95% CI 0.19-0.73 with H2- receptor blockers) (35). Furthermore, combination treatment with H2 receptor blocker and aspirin caused less inhibition of platelet aggregation than aspirin alone (p = 0.02 compared with aspirin alone) (36). Studies comparing the efficacy of misoprostol and lansaprozole indicated that misoprostol 800 mcg, lansoprazole 15 mg or 30 mg reduced the risk of gastric and/or duodenal ulcer recurrence at similar rates, nevertheless, misoprostol group experienced slightly more side effects including diarrhea and compliance problems (37, 38). Therefore, lansoprazole is believed to have several theoretical and practical advantages over misoprostol. There have been no studies of comparing different PPIs with each other. However, considering that they have the same mechanism of action, it can be speculated that all would have similar preventive power against relapsing ulcers and gastrointestinal bleeding.

What should be done in patients with acute gastrointestinal bleeding?

The classical treatment algorithm for acute upper gastrointestinal bleeding is ceasing the antiplatelet treatment, eradicating H. pylori infection if positive, endoscopic coagulation and high dose proton-pump inhibitor therapy introduction. The reintroduction of anti-platelet therapy might be done after 8 weeks following ulcer healing. However, this might not be the case in patients with high cardiovascular risk. Since cardiovascular mortality could increase in such patients, antiplatelet treatment should be initiated as soon as possible. Reintroduction of aspirin and switching to another anti-platelet agent such as clopidogrel are the possible options but there are no trials comparing these agents' safety in such patients. In a recent double blind trial, 113 aspirin receiving patients with acute gastrointestinal bleeding were randomized to receive either aspirin 80 mg/d or placebo immediately after successful endoscopic coagulation. All patients receive concurrent PPI treatment as well. Recurrent bleeding rate, hospital stay and transfusion requirement did not differ between 2 groups while mortality rates at 1st and 2nd month are lower in aspirin group (39). Based on these results, it seems safe to reintroduce antiplatelet treatment with concurrent PPI use immediately after successful endoscopic coagulation. Further studies are needed to compare different anti-platelet agents in this setting.

How long PPI treatment should be continued in high risk patients?

Indeed the optimal duration of PPI treatment in high risk patients has not been tested in randomized clinical trials. However, since no serious adverse effects of long-term PPI treatment have been reported, it seems reasonable for high risk patients to take PPI treatment as long as they take aspirin. On the other hand, duration of PPI treatment in low risk patients is questionable.

Conclusion

- Aspirin treatment, even in low doses, increases peptic ulcer formation, gastrointestinal bleeding and gastrointestinal symptoms such as dyspepsia;
- Enteric coated forms of aspirin do not reduce the risk of peptic ulcer formation and gastrointestinal bleeding;
- Results from initial studies with NO - donating aspirin are promising, but further studies are needed to clarify their preventive effects against ulcer formation and gastrointestinal bleeding in long term use;
- There are several factors increasing the risk of peptic ulcer formation and bleeding from the ulcers including older age, previous ulcer or bleeding history, concomitant NSAID, steroid or other anti-platelet drug use and H. pylori infection;

• H. Pylori should be eradicated in high risk patients;

• In patients with high risk for gastrointestinal bleeding, PPI should be added to the treatment to reduce the risk of ulcer and gastrointestinal bleeding recurrence;

• The optimum duration of concurrent PPI treatment has not been tested in aspirin users with high risk of gastrointestinal bleeding.

References

1. Vane J. The mechanisms of action of aspirin like drugs in aspirin - medicine of the century. Proceedings of the Centennial Anniversary of Aspirin Symposium, April 20-24, Venice, Italy 1997.
2. Gibson PC. Aspirin in the treatment of vascular diseases. Lancet 1949; 2:1172-4.
3. Douthwaite AH, Lintott, S.A.M. Gastroscopic observation of the effect of aspirin and certain other substances on the stomach. Lancet 1938; 2: 1222-5.
4. Lanas A. Cyclo-oxygenase-1/cyclo-oxygenase-2 non selective non-steroidal anti-inflammatory drugs: epidemiology of gastrointestinal events. Dig Liver Dis 2001; 33 Suppl 2: S29-34.
5. 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.
6. Liberopoulos EN, Elisaf MS, Tselepis AD, Archimandritis A, Kiskinis D, Cokkinos D, et al. Upper gastrointestinal haemorrhage complicating antiplatelet treatment with aspirin and/or clopidogrel: where we are now? Platelets 2006; 17:1-6.
7. Buerke M, Pittroff W, Meyer J, Darius H. Aspirin therapy: optimized platelet inhibition with different loading and maintenance doses. Am Heart J 1995; 130: 465-72.
8. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71-86.
9. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA 2007; 297: 2018-24.
10. Slattery J, Warlow CP, Shorrock CJ, Langman MJ. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin -analysis of gastrointestinal bleeding during the UK-TIA trial. Gut 1995; 37:509-11.
11. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group. N Engl J Med 1991; 325:1261-6.
12. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol 2005; 95: 1218-22.
13. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ 2000; 321: 1183-7.
14. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352: 1293-304.
15. Dammann HG, Burkhardt F, Wolf N. Enteric coating of aspirin significantly decreases gastroduodenal mucosal lesions. Aliment Pharmacol Ther 1999; 13:1109-14.
16. Cole AT, Hudson N, Liew LC, Murray FE, Hawkey CJ, Heptinstall S. Protection of human gastric mucosa against aspirin-enteric coating or dose reduction? Aliment Pharmacol Ther 1999; 13: 187-93.
17. Sorensen HT, Mellemkjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000; 95: 2218-24.
18. de Abajo FJ, Garcia Rodriguez LA. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. BMC Clin Pharmacol 2001;1:1.
19. Wallace JL, Muscara MN, McKnight W, Dicay M, Del Soldato P, Cirino G. In vivo antithrombotic effects of a nitric oxide-releasing aspirin derivative, NCX-4016. Thromb Res 1999; 93: 43-50.
20. Fiorucci S, Santucci L, Cirino G, Mencarelli A, Familiari L, Soldato PD, et al. IL-1 beta converting enzyme is a target for nitric oxide-releasing aspirin: new insights in the antiinflammatory mechanism of nitric oxide-releasing nonsteroidal antiinflammatory drugs. J Immunol 2000; 165: 5245-54.
21. al-Swayeh OA, Clifford RH, del Soldato P, Moore PK. A comparison of the anti-inflammatory and anti-nociceptive activity of nitroaspirin and aspirin. Br J Pharmacol 2000; 129: 343-50.
22. Fiorucci S, Santucci L, Gresele P, Faccino RM, Del Soldato P, Morelli A. Gastrointestinal safety of NO-aspirin (NCX-4016) in healthy human volunteers: a proof of concept endoscopic study. Gastroenterology 2003; 124: 600-7.
23. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol 1998; 93: 2037-46.
24. Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment Pharmacol Ther 2002;16: 1945-53.
25. Weil J, Langman MJ, Wainwright P, Lawson DH, Rawlins M, Logan RF, et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut 2000; 46: 27-31.
26. Loke YK, Bell A, Derry S. Aspirin for the prevention of cardiovascular disease: calculating benefit and harm in the individual patient. Br J Clin Pharmacol 2003; 55: 282-7.
27. Aalykke C, Lauritsen JM, Hallas J, Reinholdt S, Krogfelt K, Lauritsen K. Helicobacter pylori and risk of ulcer bleeding among users of nonsteroidal anti-inflammatory drugs: a case-control study. Gastroenterology 1999; 116: 1305-9.
28. Cullen DJ, Hawkey GM, Greenwood DC, Humphreys H, Shepherd V, Logan RF, et al. Peptic ulcer bleeding in the elderly: relative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs. Gut 1997; 41: 459-62.
29. Santolaria S, Lanas A, Benito R, Perez-Aisa M, Montoro M, Sainz R. Helicobacter pylori infection is a protective factor for bleeding gastric ulcers but not for bleeding duodenal ulcers in NSAID users. Aliment Pharmacol Ther 1999;13: 1511-8.
30. Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med 2001; 344:967-73.
31. Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Effects of Helicobacter pylori and nonsteroidal anti-inflammatory drugs on peptic ulcer disease: a systematic review. Clin Gastroenterol Hepatol 2006; 4: 130-42.
32. Ji KY, Hu FL. Interaction or relationship between Helicobacter pylori and non-steroidal anti-inflammatory drugs in upper gastrointestinal diseases. World J Gastroenterol 2006; 12: 3789-92.
33. Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ 2006; 333:726. Epub 2006 Sep 19.
34. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev 2002; 4: CD002296.
35. Lanas A, Garcia-Rodriguez LA, Arroyo MT, Bujanda L, Gomollon F, Forne M, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007; 102: 507-15.
36. Lev EI, Ramabadran RS, Guthikonda S, Patel R, Kleiman A, Granada JF, et al. Effect of ranitidine on the antiplatelet effects of aspirin in healthy human subjects. Am J Cardiol 2007; 99:124-8.
37. Goldstein JL, Huang B, Amer F, Christopoulos NG. Ulcer recurrence in high-risk patients receiving nonsteroidalanti-inflammatory drugs plus low-dose aspirin: results of a post HOC subanalysis. Clin Ther 2004; 26:1637-43.
38. Graham DY, Agrawal NM, Campbell DR, Haber MM, Collis C, Lukasik NL, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. Arch Intern Med 2002;162:169-75.
39. Sung J, Lau J, Ching J, Leung WK, Lee YT, Wu J, et al. Can aspirin be reintroduced with proton pump inhibitor infusion after endoscopic hemostasis? A double blinded Randomized Controlled Trial. Gastroenterology 2006;130 (Suppl 2): A134. (Abstr.).