Coated Aspirin Does Not Confer Benefit

de Abajo FJ, Garcia Rogriguez 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.

Study Overview

Objective. To estimate the risk of upper gastrointestinal bleeding (UGIB) with use of regular aspirin versus enteric-coated aspirin.

Design. Case-control study using data from the U.K. General Practice Research Database [1].

Setting and participants. Patients aged 40 to 79 years with a clinical diagnosis of peptic ulcer disease or a specific site of bleeding / perforation located in the duodenum or stomach. Only patients who were referred to a specialist or admitted to the hospital were retained as cases. The date of first diagnosis was used as the index date. Patients were excluded who had liver disease, malignancies, coagulopathies, alcoholism, Mallory-Weiss disease, or esophageal varices in the 2 months after the index date. Controls were matched for age, sex, and calendar year and were excluded according to the criteria used for case patients.

Exposures. Patients were identified as current users if their supply of an aspirin prescription lasted until the index date or ended within 30 days before the index date, recent users if their supply ended between 31 and 180 days before the index date, and past users if their supply ended more than 180 days before the index date. Nonusers were patients for whom an aspirin prescription was never recorded before the index date. Among current users, treatment duration, type of preparation, and dose effects were studied. Daily doses were estimated based on prescriptions and intervals between prescriptions. Exposure to other agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, steroids, anticoagulants, selective serotonin reuptake inhibitors, and antiulcer medications (antacids, histamine$_2$ [H_2] blockers, omeprazole) were also evaluated.

Main outcome measures. UGIB and perforation.

Main results. 1833 cases of UGIB and 272 cases of perforation were identified, and 11,500 controls were selected. In a random sample of 100 cases, most indications for aspirin were secondary prevention of cardiovascular events. Among UGIB cases, 44% of lesions were in the duodenum, 42% in the stomach, and 14% in an unspecified location; 4.1% of UGIB cases were fatal. Among perforation cases, 13% occurred in the stomach and 87% in the duodenum, with a case-fatality rate of 21%. Current users of aspirin comprised 13.5% of UGIB cases and 14.3% of perforation cases compared with 7.3% of controls (adjusted relative risk [RR] for all cases, 2.0 [95% confidence interval {CI}, 1.7 to 2.3]). No significant differences were observed when UGIB and perforation were considered as separate outcomes or when lesion location was taken into account. Risk was essentially the same for fatal (RR, 1.8 [95% CI, 1.1 to 2.9]) and nonfatal (RR, 2.0 [95% CI, 1.7 to 2.4]) events, and no modification of RR estimates was seen by sex (for males, 2.0 [95% CI, 1.6 to 2.4]; for females, 2.0 [95% CI, 1.5 to 2.6]). By age-group, RRs were 2.4 (95% CI, 1.3 to 4.4) for ages 40 to 59 years, 2.3 (95% CI, 1.8 to 3.1) for ages 60 to 69 years, and 1.8 (95% CI, 1.4 to 2.2) for ages 70 to 79 years.

Enteric-coated aspirin was associated with a risk of upper gastrointestinal complications (RR, 2.3 [95% CI, 1.6 to 3.2]) similar to that of plain aspirin (RR, 1.9 [95% CI, 1.6 to 2.3]). No statistical differences in these risks were found when bleeding and perforation or gastric and duodenal sites were analyzed separately. On the assumption that patients at high risk for gastrointestinal damage may have been prescribed enteric-coated aspirin preferentially, a subgroup analysis was performed including only patients without previous upper gastrointestinal disorder; results of this analysis were comparable to overall risk findings (RR for enteric-coated aspirin, 2.7 [95% CI, 1.7 to 4.2]; RR for plain aspirin, 2.2 [95% CI, 1.8 to 2.8]). Risk of UGIB was higher during the first 2 months of aspirin use (RR, 4.5 [95% CI, 2.9 to 7.1]), and concomitant use of high-dose NSAIDs increased UGIB risk substantially (RR, 13.3 [95% CI, 8.5 to 20.9]). No interactions were seen when low-dose aspirin was taken with low- or medium-dose NSAIDs (RR, 2.2 [95% CI, 1.0 to 4.6]).

Conclusion. In the general population, low-dose aspirin use increases risk for upper gastrointestinal complications by twofold, and the agent's coating does not modify this effect.

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An especially high risk for complications is associated with concomitant use of low-dose aspirin and high-dose NSAIDs.

Commentary

Enterocoated aspirin has previously been thought to lower risk for UGIB among aspirin users. It was assumed that the toxic effect of acetylsalicylic acid could be decreased by preventing direct contact with gastric mucosa. However, systemic effects through interaction with the prostaglandin cascade also mediate gastric toxicity, and the minimum safest dose of aspirin remains unknown. This case-control study, which begins to addresses some of these issues, was well designed. Only patients with clear documentation of gastrointestinal bleeding were included, and the presence of comorbidities as well as prescriptions for aspirin and other drugs such as NSAIDs were reviewed carefully. Despite the precautions taken, potential problems inherent to case-control trials persist in de Abajo and colleagues' work. Some confounding variables may not have been measured; for example, information concerning alcohol consumption was available for only 58% of patients. Interestingly, this study indicates that risk for gastrointestinal bleeding decreases slightly with age, while other research has shown an association between increased age and bleeding risk with NSAID use [2]. The authors did not have an explanation for this finding. Also, use of cytoprotective agents, such as H_2 blockers, antacids, and proton pump inhibitors, did not seem to provide any protective benefits according to de Abajo et al's results. Researchers were able to detect a dose-effect relationship when examining regular aspirin but could not find such an association for the enteric-coated preparation.

Applications for Clinical Practice

In general, risk for gastrointestinal bleeding is around 1% to 2% for patients using NSAIDs on a regular basis [3]. Based on such evidence, physicians may be tempted to prescribe enteric-coated aspirin or low-dose aspirin to decrease risk of upper gastrointestinal complications. However, given the results of this study, use of enteric-coated aspirin does not seem justifiable. Patients should be advised about the similar risks associated with plain aspirin and its "safer" preparations. Further, with the wide availability of NSAIDs over the counter, patients should be specifically counseled about the potentially hazardous combination of aspirin and NSAIDs in high doses.

References

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3. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs [published erratum appears in N Engl J Med 1999;341:548]. N Engl J Med 1999;340:1888–99.