Critical Appraisal

Preventing recurrent ulcer bleeding

Switch from acetylsalicylic acid to clopidogrel or add esomeprazole?

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Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352(3):238-44.

Research question

Is clopidogrel as effective as acetylsalicylic acid plus esomeprazole for preventing recurrent ulcer bleeding in patients with a history of upper gastrointestinal (GI) bleeding due to ASA therapy?

Type of article and design

Prospective, randomized, double-blind, noninferiority trial.

Relevance to family physicians

A common clinical dilemma is how to manage patients with a history of GI bleeding who need ASA to prevent vascular events. A small study found that patients with a history of bleeding ulcers who continued to take ASA had as high as 15% (95% confidence interval [CI] 7% to 25%) risk of recurrent bleeding within a year.[1] Even though using proton pump inhibitors (PPIs) for patients with a history of bleeding ulcers is known to prevent recurrent ulcers and reduce complications,[1] adding another medication to these patients' regimens might reduce compliance and will increase costs for those already taking ASA.

Current cardiology guidelines recommend clopidogrel as an alternative for patients with serious GI intolerance of ASA.[2] This recommendation is based largely on the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, which showed that clopidogrel was marginally more effective than ASA at preventing ischemic events and was associated with a lower rate of GI bleeding (0.5% vs 0.7%) over 3 years.[3] Chan et al were the first to run a prospective trial comparing the effects of clopidogrel on the GI system with the effects of ASA plus a PPI on the GI system.

Overview of study and outcomes

Patients who had bleeding ulcers while they were taking ASA were recruited from a single centre in Hong Kong. All patients had endoscopic confirmation that their ulcers had healed and that they were not infected with *Helicobacter pylori*. Patients were excluded if they were taking concomitant medications that increased risk of ulcer bleeding, had a history of gastric surgery or other GI complications, suffered renal failure, or had allergies to ASA or clopidogrel. Eligible patients were randomly allocated to 75 mg of clopidogrel daily plus placebo twice daily or 80 mg of ASA daily plus 20 mg of esomeprazole twice daily for 12 months. The primary end point was recurrent ulcer bleeding as defined by specific criteria.

Results

Of the 492 patients screened, 320 were enrolled in the study. Of these, 161 were given clopidogrel, and 159 were given ASA plus esomeprazole. Patients were an average of 72 years old; 67% were male. Risk factors for GI bleeding included previous bleeding from gastric or duodenal ulcers (88.2%), current alcohol consumption (8.1%), and reduced renal function (30.4%). Median duration of follow-up was 12 months (range 0.3 to 12 months). Compliance was high; 94% of patients in each group took at least 80% of the assigned study drug. Drop-out rates after 1 year were similar in both groups (11.8% in the clopidogrel group and 8.8% in the ASA plus esomeprazole group).

Patients given clopidogrel had a significantly higher risk of recurrent ulcer bleeding than patients given ASA plus esomeprazole (8.6% vs 0.7%, a difference of 7.9% [95% CI 3.4% to 12.4%], $P=.001$; number needed to harm = 13). Risk of lower GI bleeding was similar in both groups (4.6%, $P=.98$).

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Analysis of methodology

A strength of this study is its minimization of systematic bias by ensuring that confounders were equally distributed between groups during randomization. Blinding was adequately maintained with a double-dummy design using placebo in place of esomeprazole. Intention-to-treat analysis preserved the value of randomization by limiting the determinants under study to the treatment assignment.

The two groups were comparable at baseline with respect to risk factors for GI ulceration and bleeding. Throughout the trial, both groups had similar treatment administration schedules, follow-up assessments, and restrictions on use of other medications. Rates of treatment discontinuation were low, compliance was high, and follow-up was complete for all but three patients. End points were assessed by an independent adjudication committee using specific criteria. Recurrent ulcer bleeding was confirmed by endoscopy. To ensure that bleeding was attributable to treatment, only events that occurred during treatment or within 28 days of discontinuing treatment were analyzed.

The study had several limitations. Study drugs were repackaged from their commercial form to maintain blinding, which could have affected drug absorption and attenuated the ulcer-inducing effects of ASA. The optimum dose of esomeprazole for preventing ASA-induced bleeding is unknown. The authors justified twice-daily dosing of 20 mg because of the unacceptably high rates of recurrent GI bleeding that occurred with once-daily PPI dosing in a previous study.[1,4] Also, the predominantly Chinese study population might not represent the general population in Canada because Chinese people metabolize esomeprazole differently from other ethnic groups. About 13% to 23% of the Chinese population metabolize esomeprazole poorly through the CYP-2C19 liver enzyme, which leads to higher concentrations of esomeprazole in their systems and greater therapeutic effect.[5] In practice, patients with a history of GI bleeding might not be assessed or treated routinely for *H pylori* before they receive antiplatelet therapy. Despite its limitations, this study makes a compelling case for revisiting the guidelines on vascular protective therapy for patients at high risk of recurrent GI bleeding.

Application to clinical practice

This study demonstrates that clopidogrel might not be a safe alternative to ASA for patients with a history of GI bleeding. These findings should be considered along with findings from the CAPRIE study that show clopidogrel to be only marginally superior to ASA for vascular protection.[3,6] This study by Chan et al confirms the gastroprotective effect of esomeprazole for patients taking low-dose ASA. The combination of ASA and esomeprazole appears to be well tolerated and to be associated with minimal risk of bleeding. This treatment combination is more expensive than clopidogrel in Canada, but its benefits likely justify the added cost for high-risk patients. Recognizing that the gastroprotective effects of esomeprazole might not be directly generalizable to non-Chinese people, specific strategies for prescribing antiplatelet therapy for patients at high risk of recurrent GI bleeding include:

- using the lowest effective dose of ASA (81 mg) in combination with esomeprazole (if a class effect is assumed, equivalent doses of another PPI can be substituted for esomeprazole);
- considering baseline GI risk factors (history of ulcer or GI complications, age, congestive heart failure, concurrent anticoagulant or corticosteroid therapy) when assessing the need for gastroprotective therapy; and
- identifying patients with a history of ulcer-related bleeding from ASA who are taking clopidogrel and considering switching them to ASA plus esomeprazole.

Bottom line

- Current recommendations for using clopidogrel for patients with a history of ulcer-related bleeding

are based on the CAPRIE trial, but CAPRIE was not designed to compare GI safety, used a relatively high dose of ASA (325 mg), and excluded patients with a history of GI bleeding.[3]

- Chan et al evaluated the safety of antiplatelet therapies in patients with a history of ulcer-related bleeding and found that clopidogrel led to more bleeding than ASA plus esomeprazole did.
- For patients with a history of bleeding ulcers who require antiplatelet therapy, adding esomeprazole to ASA might be safer than switching to clopidogrel.

Points saillants

- Les recommandations actuelles en faveur du clopidogrel chez les patients ayant des antécédents d'hémorragies causées par des ulcères se fondent sur l'étude CAPRIE, mais cette étude n'était pas conçue pour comparer la sécurité GI, prévoyait une dose relativement élevée d'AAS (325 mg) et excluait les patients ayant des antécédents d'hémorragie GI[3].
- Chan *et al.* ont évalué l'innocuité des thérapies antiplaquettaires chez les patients ayant des antécédents d'hémorragies reliées aux ulcères et ont trouvé que le clopidogrel causait plus d'hémorragies que l'AAS plus l'ésoméprazole.
- Pour les patients ayant des antécédents d'ulcères hémorragiques qui doivent suivre une thérapie antiplaquettaire, il pourrait être plus sécuritaire d'ajouter de l'ésoméprazole à l'AAS que de prendre du clopidogrel.

References

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