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Washington University Emergency Medicine Journal Club
Proton Pump Inhibitors in Upper GI Bleeds

Vignette

You're working a shift in EM-2 one day when you pick up a patient with the chief complaint of "bloody emesis." The patient is a 45 year old male with a history of chronic low back pain who takes daily naproxen (250 mg BID). His pain worsened two months ago when he was in an MVC, and he has been taking ibuprofen in addition to the naproxen. He began noticing epigastric abdominal discomfort 3 weeks ago, and last night began vomiting up coffee-ground emesis. This morning he had one episode of bright right emesis and decided to come to the ED.

He is hemodynamically stable, appears to be in no distress, and is not actively vomiting. He has mild epigastric abdominal tenderness, clear lungs, normal heart sounds without tachycardia, and his conjunctiva and skin do not appear to be pale. His hemoglobin is 13 and his PT/INR and PTT are normal. An NG tube is placed and returns coffee grounds with streaks of blood that do not clear after lavage with one liter of normal saline. You order a type and screen and cross him for 4 units (just in case).

You call the GI fellow, thinking that the patient probably needs an upper endoscopy. The GI fellow asks that you start the patient on a continuous infusion of intravenous pantoprazole. You wonder how useful IV proton pump inhibitors actually are in the setting of upper GI bleeds, and whether a continuous infusion (which ties up an IV and is rather expensive) is really necessary. The patient is admitted to the ICU with plans for an EGD later in the day. After you leave your shift you decide to look and see if there is any evidence out there on the use of PPIs in the management of acute upper GI hemorrhage.

PICO Question
Population: Adult patients with undifferentiated acute upper GI bleeding
Intervention: Proton pump inhibitor (either IV or PO)
Comparison: Placebo
Outcome: Mortality, rebleeding rates, need for surgery, need for blood transfusion, ICU length of stay, hospital length of stay

Search Strategy

A search of the Cochrane database using the term “proton pump inhibitor” resulted in a relevant meta-analysis from 2010. A search of PubMed using the strategy ("proton pump inhibitor" OR omeprazole OR pantoprazole OR esomeprazole OR lansoprazole) AND (bleed OR bleeding OR hemorrhage), limited to clinical trials in the last 5 years, yielded no additional relevant articles (http://tinyurl.com/q32oyaf). Three articles included in the Cochrane review were therefore chosen.

Article 1: Hawkey GM, Cole AT, McIntyre AS, Long RG, Hawkey CJ. Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. Gut. 2001 Sep;49(3):372-9. Answer Key.

Article 2: Dorward S, Sreedharan A, Leontiadis GI, Howden CW, Moayyedi P, Forman D. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005415. Review. Update in: Cochrane Database Syst Rev. 2010;(7):CD005415. Answer Key.

Article 3: Lau JY, Leung WK, Wu JC, Chan FK, Wong VW, Chiu PW, Lee VW, Lee KK, Cheung FK, Siu P, Ng EK, Sung JJ. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med. 2007 Apr 19;356(16):1631-40. Answer Key.

Article 4: Daneshmend TK, Hawkey CJ, Langman MJ, Logan RF, Long RG, Walt RP. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. BMJ. 1992 Jan 18;304(6820):143-7. Answer Key.

Bottom Line

The efficacy of proton pump inhibitors in the acute management of upper GI bleeding, prior to endoscopy, has been debated since the 1990s, as evidenced by several randomized controlled trials from that decade (Daneshmend 1992, Hulagu 1995, Wallner 1996). Twenty years later, the debate rages on. Many resources, including UpToDate, recommend initiating proton pump inhibitor therapy prior to endoscopy, whereas others have recommended that they not be used routinely.

Much of this debate stems from a Cochrane systematic review and meta-analysis published on the subject in 2006, and later revised in 2010. In this systematic review, the authors found no effect on mortality (OR 1.12, 95% CI 0.75 to 1.68), rates of rebleeding (OR 0.81, 95% CI 0.62 to 1.06), the need for surgery (OR 0.90, 95% CI 0.65 to 1.25), or the need for a transfusion (OR 0.95, 95% CI 0.78 to 1.16). Despite this lack of a reduction in any patient-important outcomes, they did find a significant reduction in the stigmata of recent hemorrhage at endoscopy (OR 0.67, 95% CI 0.54 to 0.84). The main argument, therefore, stems from the acceptance of certain surrogate outcomes in place of patient-important outcomes.

In fact, the articles referenced in the meta-analysis tended to find similar results individually. Daneshmend et al (1992) found no difference in mortality, rebleeding, or need for transfusion, but noted a decrease in signs of bleeding at endoscopy. Hawkey et al (2001) found no reduction in death or rebleeding, but found a significant reduction in the presence of blood in the stomach at endoscopy. Finally, Lau et al (2007) found no difference in death or need for surgery, but did find a reduction in the need for treatment at the time of endoscopy (though all patients underwent endoscopy).

Surrogate outcomes have long been used in clinical research, offering several advantages such as lower cost, smaller sample size, and shorter follow-up. However, caution must be used when employing such outcomes. A validation is required before correlating an improvement in a surrogate outcome with an improvement in

a patient-centered outcome. Complex statistical formulae have been proposed to make such a validation, such as those proposed by Prentice in 1987, but even these criteria have been called into question (Berger 2004). Equally important is the issue of determining the effect size for a patient-important outcome by using a surrogate outcome, even when the two have been shown to correlate. It has been shown, for example, that the use of surrogate outcomes tends to result in an overestimation of effect size when compared to studies using patient-important outcomes.

By demonstrating an improvement in surrogate outcomes without improvements in patient-important outcomes, the authors of these studies and of the Cochrane review all draw similar conclusions: that the data is limited but suggest that there may be a benefit to using a proton pump inhibitor for upper GI bleeds. The American College of Gastroenterology draws a similar conclusion in its guideline: "Pre-endoscopic intravenous proton pump inhibitor (PPI)…may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. However, PPIs do not improve clinical outcomes such as further bleeding, surgery, or death (Conditional recommendation, high-quality evidence)." This recommendation seems reasonable, and given the few downsides to proton pump inhibitors, their administration is likely worthwhile, as long as it does not interfere with other, potentially more important, interventions (i.e. resuscitation of critically ill patients, reversal of anticoagulation, or blood transfusion in symptomatic anemic patients).