Editorial

Primary and secondary prevention of non-variceal upper gastrointestinal bleeding: use or abuse?

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In this edition of the magazine Dr. Castro Herrera and Dr. Bejarano Escandon warn us about the use of prophylactic drugs for non-variceal upper gastrointestinal bleeding (1). They briefly evaluate iatrogenesis, in this case the role of self-prescribed and physician-prescribed medications as important causal factors of non-variceal upper gastrointestinal bleeding. In addition they question the use of expensive drugs, which may have unwanted side effects, in a country such as ours with restricted economic resources. They raise the alarm in regard to our current use of these drugs and question whether or not we are making good use of them.

Although Swan first described acute stomach and duodenal ulcers in patients with serious burns in 1823, the first case histories of 10 patients were published by Curling in 1842. Ulcers became the most common and dreaded gastrointestinal complication for burn patients. Up to 12% of severely burned patients, those with burns over more than 30% of their bodies, develop ulcers. Bleeding is the initial manifestation in two thirds of these patients. Similar symptoms, called Cushing ulcers, have been found in trauma patients undergoing encephalocranial or central nervous system surgery. Stress ulcers, which have high mortality rates, are found in other critically ill patients (2).

Global morbidity and mortality rates for non-variceal upper gastrointestinal bleeding have not fallen in the last 30 years, but rather have remained at levels around 6% to 7%. Possibly this is due to increasing numbers of older patients and increased numbers of concurrent illnesses, both predictors of poor prognoses (3). To this we should we add the roles that ASA and NSAIDs play. In the article from the Clinica Rafael Uribe Uribe these medications are key risk factors for the development of bleeding in 27.5% of patients in the study. It is known that about 25% of all patients taking these drugs develop adverse gastrointestinal effects. Complications are dose dependent and have a higher rate in the first month of use. It has also been found that patients over the age of 65 have higher risk for the development of this gastroenteropathy. Risk factors include age, history of complicated peptic ulcer disease, previous gastrointestinal bleeding, associated cardiovascular disease, and concomitant use of ASA, antiplatelet agents or Warfarin. The potential risks from greater numbers of factors, particularly if there has been a history of a complicated peptic ulcer, could motivate the prescription of a change for selective COX-2 selective inhibitor with or without proton pump inhibitor instead of other NSAIDs as the primary prophylaxis. A short corticosteroid cycle might be prescribed if anti-inflammatories are required, or if analgesia is required, ASA can be replaced with Acetaminophen alone or combined with codeine or tramadol. The role of corticosteroids remains controversial, but apparently risk has been reported when

used at moderately high doses, especially if concomitant with the use of ASA / NSAID when the risk is 2 times greater. The use of oral anticoagulants alone creates a 3.3% risk of bleeding, but that number increases to 12.7% when oral anticoagulants are combined with NSAIDs (4).

The term stress-related mucosal disease is most commonly used to refer to conditions ranging from injury-related stress (superficial mucosal damage) to stress ulcers (focal deep mucosal damage). The pathophysiology of this entity is unclear, but it can occur rapidly after a severe event such as trauma, surgery, sepsis or burns. In 75% to100% of patients, it occurs within 24 hours of ICU administration (5-7).

The European Society of Intensive Care Medicine (ESICM) suggests that the following factors are associated with increased risks: mechanical ventilation lasting longer than 48 hours, presence of coagulopathy, neurosurgery, and any kind of shock, sepsis, polytrauma, quadriplegia, severe burns, and organ failure. It has also added a history of gastric or duodenal ulcer, liver cirrhosis and renal failure.

A recent meta-analysis by the Eastern Association for the Surgery of Trauma (EAST) looked at articles analyzing risk factors and for patients who need prophylaxis. Of 119 articles, 46 good quality studies were selected, including 27 with high-value evidence-based medicine. Based on their analysis they make a Level 1 recommendation for all patients on mechanical ventilation, or who have coagulopathy, traumatic brain injuries and major burns. Their recommendations are level 2 for patients with multiple trauma, sepsis and renal failure and level 3 for cases of APACHE II Score, high ISS (injury Severity Score), and patients who require high-dose corticosteroids. Their recommendations for medications to use are as follows: Level 1 recommendation for proton pump inhibitors, H2 receptor antagonists and cytoprotective agents; Level 2 recommendation not to use aluminum compounds in dialysis patients; Level 3 recommendation that initiation of tube feeding alone is insufficient because of the slight increase in pH, despite its protective role must be considered only as an adjunct. With regard to medication time there is no level 1 recommendation; the Level 2 recommendation continues during mechanical ventilation or while patient is in an ICU. The Level 3 recommendation continues for as long as the patient tolerates tube feeding, although some recommend its use for no more than a week. However, there is consensus that the duration should be individualized (16).

The most important reference work was that of Dr. D.J. Cook who found incidences of major bleeding in 1.5% out of 2252 patients in his study. OR was 15.6 in cases of respiratory failure, 4.3 in patients with coagulopathy. 3.7% of patients with risk factors presented major bleeding, compared with 0.1% of patients with no risk factors. Mortality was 48.5% for those patients who suffered from bleeding and only 9.1% for those without this complication (8, 9). In other studies the figures were similar, averaging 2.6% in the 27 high value papers. These and other publications have indicated that coagulopathy and respiratory failure are associated with higher risks (6, 7). These findings are consistent with those observed in the Clinica Rafael Uribe Uribe study in Cali, but with a bleeding rate of 3 to 7 times higher in this study for high risk patients (12.2%), thus the emphasis is on identifying risk groups for not obviate the need for prevention, as even a quarter of them were in danger without their treatment (25.6%).

In assessing the usefulness of prophylactic medication, the publications have suggested that patients who are not receiving mechanical ventilation or coagulopathy are usually at low risk, between 0.1% and 0.5%. As in the present study, 20.1% received prophylaxis. If these drugs reduce the risk by 50%, an NNT of 900 would be required to prevent significant bleeding. The risk of bleeding in high risk groups is usually between 2% and 3.7%, therefore the benefits for this group would be much greater, with an NNT of 30. Consequently restricting prophylaxis if at least one of these risk factors is present in critically ill patients would be a good recommendation to follow (7).

The aim of this treatment is to maintain pH greater than 4 in order to decrease back-diffusion of hydrogen ions and deactivate pepsin. The percentage of time during the day in which this high pH is maintained is important. Increased intragastric pH apparently has not been associated with increased incidence of nosocomial pneumonia. According to a meta-analysis published about the use of ranitidine as an antisecretory agent, it had an incidence of 19.1% compared to the incidence rate with acid neutralizers such as sucralfate of 16.2%. Very simple measures such as elevating the head of the bed can reduce the development of this respiratory complication by 30% or more (11, 13).

When choosing medication, it is essential to keep in mind that overall 195 of ICU patients have liver dysfunction and 40% have renal dysfunction. However, when patients have sepsis these figures jump to 73% and 60% respectively (11).

Misoprostol has not shown any benefits for prophylaxis of stress-related mucosal disease, but it does have a role in primary and secondary prophylaxis of ASA/NSAID induced gastroenteropathies (10).

Sucralfate protects the gastric mucosa without raising pH, but it can only be used orally or through mouth tubes or nasogastric feeding tubes (NG tubes). The usual dose is 1 gm every 6 hours. Side effects which have been described included constipation, tube blockage, bezoars and hypophosphatemia. If renal dysfunction is present patients can

develop aluminum toxicity. This drug has been found to decrease absorption of warfarin, phenytoin, digoxin, quinidine and fluoroquinolones, affecting their effect (10, 11).

Administration of antacids through an NG tube is required every 1 or 2 hours, at volumes highly dependent on the intragastric pH determination. Their use requires monitoring and certification since it has the potential for aluminum toxicity, electrolyte disturbances, diarrhea, and catheter occlusion. For all of these reasons it is no longer recommended very frequently (10, 11).

H2 receptor antagonists are among the most widely used treatments (49.8% of all patients) as shown by the work of Dr. Henderson and Dr. Bejarano. However, their proven efficacy comes with significant limitations, the most significant of which is the potential for tachyphylaxis, which in this case means failure to maintain pH greater than 4 at the usual dose of 50 gm IV every 8 hours. This phenomenon is due to increased endogenous release of histamine antagonists which compete for these receptors. It usually occurs within 48 hours and can not be controlled with increased dosages since this treatment does not inhibit vagally mediated acid secretion. Consequently, it is less effective in prophylaxis after neurosurgery and encephalocranial trauma. Most frequently reported adverse effects include headaches, dizziness, diarrhea, nausea and constipation. Other adverse affects which have been reported only rarely, include thrombocytopenia, abnormal liver function, and interstitial nephritis. When renal clearance is reduced producing impaired clearance dosage adjustments are required. Cimetidine and ranitidine have the potential to inhibit the hepatic cytochrome oxidase system, although ranitidine's inhibitory effects are less than those of cimetidine. Both have the potential to increase levels of midazolam, metoprolol, nifedipine, theophylline and phenytoin. Two H2 receptor antagonists do not have this potential are nizatidine and famotidine. Neurological manifestations which have been described include dystonia, agitation and hallucinations, while cardiovascular disorders which have been described include bradycardia and hypotension after intravenous administration (10, 11, 14).

Proton pump inhibitors are the drugs of choice for most gastrointestinal disorders related to acid. They are the strongest treatments available. One of their advantages is sustained increase in pH from the first dose after intravenous or parenteral administration. Another advantage is that side effects such as headache, diarrhea, nausea, constipation, and pruritus are rare. Moreover, tachyphylaxis has not been reported with its use. Its metabolism does not require dose adjustments for the elderly, patients with kidney failure or patients with moderate liver dysfunction. Their liver metabolism goes through CYP2C19 and CYP3A4. Omeprazole decreases clearance of carbamazepine, diazepam and phenytoin while lansoprazole decreases clearance of theophylline. In Phase II Pantoprazole makes it nonsaturable, causing it to have lower potential on CYP450. In sum, since it has less drug interaction and is dose response is not linear, adjustments do not need to be made in the circumstances previously noted. Presentation is available for intravenous use of omeprazole, esomeprazole, and pantoprazole, but is not available for lansoprazole. Lansoprazole is available in syrup. Some groups recommend mixing its granules or dissolving tablets of it in a weak acid solution, such as apple juice, and administering it through an NG tube. Orally administered PPIs have proven useful in primary prophylaxis in secondary prophylaxis to decrease possible recurrence of bleeding (10-12, 14, 15).

The profile of in-vitro platelet aggregation is profoundly affected by acidic environments. At a pH between 6.8 and 7.4 it is reduced 75%. It practically disappears at pHs less than 5.9. Aggregated platelets disaggregate as pH levels fall, but they aggregate again when the pH level returns to the normal level of 7.4. H2 receptor antagonists, such as ranitidine, maintain pH levels above 4 approximately 65% of the day, but proton pump inhibitors maintain these levels for 95% of the day. While use of H2RAs fluctuates, use of proton pump inhibitors is stable at between 75% and 83% of determinations (7).

Bleeding increases a patients ICU stay from 4 to 8 days with corresponding increase in costs. In the United States, the economic impact of hospital treatment of a patient with upper gastrointestinal bleeding is about (US) $5,000.00. Based on 150,000 hospital admissions a year the total cost is (US) $750 million. The estimate for short-stay patients with gastrointestinal bleeding in Canada is (US) $ 3,000.00, taking into account that this complication increases hospital stays from 4 to 8 days. For patients over 65 years with comorbid diseases that value increases. High social costs, both in terms morbidity and financial impact, motivate optimization of the use of primary prophylaxis.

The drugs described above have similar prophylactic effects in the development of stress-related mucosal disease and in the complication of bleeding. The ideal agent should be effective in reducing risk, should have low potential for side effects and drug interactions, should have pharmacokinetic characteristics which facilitate use in patients with dysfunction of vital organs, and should be cost-effective. Cost effectiveness should extend beyond acquisition costs and availability to include the overhead costs of monitoring and management. Finally the choice of medication and duration of use should be individualized for all the reasons previously mentioned.

Each institution must establish which patients are at risk and can benefit from the use of prophylactic drugs for stress ulcers. The study from the Clinica Rafael Uribe Uribe in

Cali was the first step in understanding what happens in our country regarding the use of prophylactic drugs for primary prophylaxis against the development of non-visceral gastrointestinal bleeding. The study specifically targeted at risk patients. Despite the study's short ten-day time period for patient selection and monitoring, this could be the beginning of a line, or of several lines, of research. ICU patients can be selected and compared with patients in other services. At-risk patients such as those with major burns can be included. The local the use and abuse of primary prophylaxis in other circumstances such as ASA/NSAID gastroenteropathy can be determined. The utility and impact on cost-effectiveness of prophylaxis for this indication here in Colombia can be determined. Local studies can be undertaken assessing circumstances such as metabolic interactions with antiplatelet IBP (e.g. clopidogrel). This is an opportunity to stimulate the initiation of research in our country on the prevalence of fast or slow metabolism of PPIs and their impacts on cases in these and in other circumstances such as the eradication of Helicobacter pylori.

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