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Pharmacotherapy of Acute Non-Variceal Bleeding

Jenkins et al. [1] review the action and application of somatostatin and its analogue, octreotide. The authors of this review all have experience using somatostatin for the control of acute non-variceal bleeding. Passing thought is sometimes given these two drugs regarding their use in selected patients with refractory bleeding from any non-variceal cause and location. Their use is typically deferred for want of any convincing data to support their use and perhaps an element of uncertainty as to the expected physiologic effects of these drugs on a bleeding lesion within the upper or lower gut. We are all well versed in the standard percentages of patients with non-variceal upper GI bleeding who spontaneously stop bleeding (80%), who continue to bleed (20%), and who will die as a result of a bleeding event (10%). The authors contend that somatostatin plays a role in the management of the high-risk patient with acute non-variceal upper GI bleeding. They have also identified the insufficient data supporting the use of octreotide for the same patient group. Let us examine the evidence for the urgent use of somatostatin.

Non-variceal upper GI bleeders at high risk for rebleeding share a common problem, an exposed or visible vessel which is typically located within a mucosal defect such as an ulcer. The ulcer may be peptic, due to prior thermal injury (e.g., post-polypectomy or sphincterotomy), traumatic (e.g., Mallory-Weiss tear), or neoplastic, either benign (e.g., leiomyoma), or malignant. In patients with a Dieulafoy lesion the exposed vessel is typically

unassociated with an ulcerating process. All of these vessels will characteristically have a start-and-stop bleeding pattern depending upon the integrity of the thrombus plugging the rent in the exposed vessel. The rationale for acute interventional pharmacotherapy has therefore reflected an effort to stabilize this clot or fibrin plug. Limited anatomic data published over a decade ago demonstrated that the critical plug we speak of may become disrupted (with rebleeding) via a process involving recanalization which is in contradistinction to the more common notion that disruption is due to effects of the gastric juices immediately surrounding and bathing the nefarious arterial plug [2]. This may be the reason why control of gastric acid secretion with H₂-receptor antagonists and pH control only with antacids has failed to demonstrate benefit. However, use of proton pump inhibitors in doses capable of inducing an acidity have been demonstrated to reduce rebleeding in patients with peptic ulcers and nonbleeding visible vessels [3]. Antifibrinolytic therapy with tranexamic acid makes considerable sense in applying the rationale for thrombus stabilization to control rebleeding, but has unfortunately failed.

Where does somatostatin fit in with regard to thrombus stabilization? Somatostatin demonstrates an inhibitory effect on pepsin secretion. Jenkins et al. [1] have identified some of the potentially critical observations reported and applied these to patients with peptic ulcers: pepsin, especially pepsin 1, tends to have higher activity than in normals; the proteolytic activity of pepsin 1 persists despite

the high gastric pH, and fibrin clots in the laboratory have been demonstrated to be digested more rapidly by gastric juice with pepsins as opposed to acid alone. Chronic administration of somatostatin in dogs has also been shown to activate blood coagulation which offers a different theoretic spin on the 'plugging' of the visible vessel. There may be a niche for somatostatin in the schema of thrombus formation and plug stabilization.

Selective reduction of splanchnic blood flow and, more so, arterial vasoconstriction is the next most desirable attribute of a possible vasoactive therapeutic drug in the setting of acute bleeding from an exposed vessel, and is a challenge in the stomach and the duodenum because of the rich blood supply, especially in the latter location. Somatostatin reduces the postprandial increase in gastric splanchnic blood flow but there is no evidence that sufficient vasoconstriction can be induced with pharmacologic doses to prevent or minimize arterial bleeding. Hard evidence for more widespread vasoactive effects elsewhere in the gut are lacking.

The argument for cytoprotection in the setting of acute upper GI bleeding, once it occurs, is irrelevant as it pertains to rebleeding in the acute setting. Cytoprotection is important in the eventual healing of the acute lesion such as an ulcer. This is a time-dependent factor. Rebleeding is greatest within 48–72 h of the index event which is too short a period of time for any cytoprotective effects of somatostatin, e.g. stimulation of gastric mucus secretion, to be efficacious.

The attention of this editorial thus far has been on continued bleeding and rebleeding. Although rebleeding may be the single most important predictor of morbidity and mortality, it is the consequences of rebleeding as opposed to the threat of exsanguination that are important. The major morbidity and mortality of patients are due to myocardial and septic events, the latter primarily related to pulmonary sepsis from aspiration. Aggressive medical and intensive unit care in patients with major bleeding events is instrumental in preventing or minimizing these complications. It is of interest that somatostatin causes an increase in the lower esophageal sphincter. It is theoretically possible that somatostatin may reduce the risk for aspiration in patients with stomachs that are filled with blood, a situation that physiologically mimics the postprandial state. There is sufficient experience and evidence to support the safety of somatostatin regarding untoward cardiovascular events, unlike vasopressin.

A number of trials have compared somatostatin to placebo, an H₂ receptor antagonist, and a proton pump inhibitor in diffuse groups of patients with upper GI

bleeding and in patients with peptic ulcers. Most of these trials are now dated, having been performed in the 1980s and prior to the NIH consensus regarding bleeding peptic ulcers and endoscopic therapy which defined high-risk endoscopic findings, with some studies arguably accessible to defining endoscopic high-risk groups according to the Forrest classification of bleeding peptic ulcers [4]. The peptic ulcer groups are of most interest in the true test of the drug, more so, those patients at high risk for continued bleeding (e.g. shock) or rebleeding (visible vessels). Studies including these patients have demonstrated significant benefit in reducing rebleeding and transfusion requirements. The most recent study and the one ultimately of most interest compares somatostatin with ranitidine and omeprazole in patients with peptic ulcers containing a visible vessel [5]. The preliminary data look favorable for the effectiveness of somatostatin in preventing rebleeding. A major problem with all these studies is the small size of the patient populations. There is no substantive data to date supporting the efficacy of octreotide in the control of bleeding from peptic ulcers with or without visible vessels.

The authors of this review [1] have recommended placing vasoactive drug therapy with somatostatin within a management algorithm involving patients with non-variceal upper GI bleeding. This recommendation is based largely upon their own reported favorable experiences. Their proposal advocates early intervention with the drug akin to the patient with acute variceal bleeding and as adjunctive therapy subsequent to endoscopic therapy of high-risk lesions, continuing the drug until clinical and laboratory stabilization is apparent. If we are willing to accept the data supporting the efficacy of somatostatin in the control of bleeding, then these recommendations are intriguing.

Somatostatin may have a place as a first line of therapy in patients presenting with an acute major upper GI bleeding event and possibly any major acute GI bleeding event who satisfy high-risk criteria for continued bleeding, rebleeding, morbidity, and mortality. The patient groups best targeted include: elderly patients; patients in shock; patients with coagulopathies either from needed anticoagulation or due to disease; patients with active bleeding (hematemesis of bright red blood and clot, bright red blood via NG, hematochezia), and patients with active comorbid disease who are not surgical candidates. In this setting the drug would be initiated at the earliest opportunity upon presentation, after stabilization of altered hemodynamics is initiated, and prior to any endoscopic intervention. A large scale, multicenter randomized

study, assessing use in this manner along with its impact on hospital length of stay, would be of keen interest.

Somatostatin remains overlooked in the management of acute non-variceal upper GI bleeding. It may have a niche in the control of bleeding within certain patient groups. The authors of this review, all of whom are experienced with the use of this drug for this problem, have resurfaced an awareness of its potential. There is room for further study in well-designed large multicenter efforts.

Editor's Note

The subject 'Somatostatin in the treatment of non-variceal upper gastrointestinal bleeding' reviewed by Dr. Spencer A. Jenkins [Dig Dis 1998;16:214–224] is further examined here by Christopher J. Gostout, MD. I would like to thank Dr. Gostout and Dr. Jenkins for their valuable contributions to *Digestive Diseases*.

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