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SQUARE PHARMACEUTICALS LTD. BANGLADESH

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Administration of an alginate based gastric reflux suppressant on the bioavailability of omeprazole

Sodium Alginate and Potassium bicarbonate combination is a reflux suppressant which achieves its activity by the formation of an alginate raft which floats on top of the stomach contents and provides a physical barrier to prevent acid reflux into the oesophagus. The liquid form of Sodium Alginate and Potassium bicarbonate combination relies on the interaction of alginate with gastric acid to form a raft of near neutral pH, but Sodium Alginate and Potassium bicarbonate combination tablets form a raft by interaction of alginic acid with antacids upon chewing in mouth. Liquid Sodium Alginate and Potassium bicarbonate combination forms a strong alginate raft in vitro and that such rafts remain in the upper part of the stomach for 1-2 h in contrast to the behaviour of antacids or other alginate products. Its mode of action does not depend on absorbtion into the systemic circulation and no drug interactions are known.

Omeprazole suppress gastric secretion by specific inhibition of the H+/K+ adenosine triphosphatase enzyme system of the gastric parietal cell . The stability of omeprazole is a function of pH and it rapidly degrades in acid medium, but has acceptable stability in alkaline conditions. Absorbtion is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 h. Peak plasma concentrations of omeprazole and area under the plasma concentration versus time curve (AUC) are approximately proportional to doses up to 20 mg with high intrasubject variability. Absolute bioavailability (compared with intravenous administration) is about 30-40 percent at doses of 20-40 mg, due in large part to presystemic metabolism.

The bioavailability of omeprazole increases slightly upon repeated administration. The majority (approximately 77%) of the dose is eliminated in urine as metabolites. In patients with chronic hepatic disease, the bioavailability is increased and the plasma half-life is increased to nearly 3 h. In patients with chronic renal impairment, the disposition of omeprazole is very similar to that in healthy volunteers, although there is a slight increase in bioavailability.

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin . There have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Omeprazole may interfere with absorbtion of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts) .

In the United Kingdom and other European countries omeprazole and Sodium Alginate and Potassium bicarbonate combination are routinely prescribed and recommended either alone or in combination for symptomatic treatment of GORD and the accompanying symptoms of acid regurgitation, heartburn and indigestion. It was therefore desirable to know whether there is any interaction between the two which may affect the pharmacokinetics of omeprazole.

Material & Methods

The study was designed as a randomized, two-treatment, two-period, crossover, multiple-dose pharmacokinetic study of the omeprazole tablet in the presence and absence of the 10 per cent liquid alginate suspension. Both treatment periods were of 3 days duration, an adequate period of time for omeprazole to reach peak plasma concentrations. Subjects received one treatment in the first period of the study, followed by a standard washout period for omeprazole of 7 days before starting the second period.

Each volunteer received, in random order – Treatment A: omeprazole magnesium 20.6 mg (equivalent to omeprazole 20 mg) tablet administered orally 15 min before breakfast for 3 days, with 240 ml drinking water. Treatment B: omeprazole magnesium 20.6 mg tablet administered orally 15 min before breakfast, with 240 ml drinking water, plus 10 per cent liquid alginate suspension (10 ml, containing 1g sodium alginate and 0.2 g potassium bicarbonate) administered orally 4 times daily (30 min after meals and at bedtime) for 3 days.

Results

Twenty four out of the 26 subjects enrolled in the study completed both periods of the study. CYP2C19 polymorphism was not determined for this study population. Two of the completed subjects reported adverse events: loose motions whilst on treatment with omeprazole plus alginate (considered possibly related to treatment) and fever whilst on treatment with omeprazole only (considered unrelated to treatment).

Discussion

The formulation of omeprazole has a profound effect on its pharmacokinetics, partly because of its acid instability. Solid dosage forms are mostly presented as enteric coated granules and although these may have a similar AUC to a buffered liquid dose the peak plasma concentration is both lower and delayed. The solid dosage form of omeprazole used in this study, MUPS tablets, has however been shown to be bioequivalent to the older, more widely used, formulation of enteric coated pellets in hard gelatine capsules 17 after one and 6 days dosing. This is known to be related to the major enzyme involved in omeprazole metabolism, CYP2C19, which is deficient in some individuals, resulting in plasma concentrations and AUCs four or five times larger than in those with this cytochrome P450 isoform. It is known that the genetic variant in which CYP2C19 is deficient is much more common in Asians than in Caucasians, although this has normally been reported for Japanese, Chinese and Koreans. The pharmacokinetic parameters reported in this study are directly comparable with those obtained in a previous study known to be carried out in Indian subjects and also with those of an earlier Australian study. These contrast with several European/US studies carried out with enteric coated granules in capsules in which the repeat dose AUC was between a quarter and a fifth of the present study AUC.

There is conflicting evidence on the effect of antacids on omeprazole bioavailability from enteric coated granules. Two European studies found no effect of concomitant liquid antacids containing aluminium and magnesium hydroxides on omeprazole, whereas a Japanese study found a marked decrease in AUC from omeprazole enteric coated tablets given concomitantly with Aluminium hydroxide and Magnesium hydroxide combination granules but not with suspension. There was no bioavailability difference found in the present study when Sodium Alginate and Potassium bicarbonate combination was administered with omeprazole tablets but this may be because Sodium Alginate and Potassium bicarbonate combination has only a very weak acid neutralizing capacity and does not contain either of the antacids. Sodium Alginate and Potassium bicarbonate combination may perhaps be considered to be more similar to food, since it is given after the meal and forms floating gelatinous mass which is retained in stomach. The effect of food on the bioavailability of omeprazole is to delay absorbtion of the drug but without affecting overall availability.

In the present study, the omeprazole was administered 15 min before a breakfast and the Sodium Alginate and Potassium bicarbonate combination 30 min after the breakfast. The results showed that the administration of Sodium Alginate and Potassium bicarbonate combination had no effect on the plasma level curve and that it therefore did not add to the effect of the meal on omeprazole absorbtion from MUPS tablets.

As the 90 per cent confidence intervals for Cmax, AUC 0-t, and AUC o-a are all contained within the bioequivalence interval of 80-125%, it can be concluded that the co-administration of this liquid alginate suspension, which has a physical mode of action and does not depend on absorbtion into the systemic circulation, has no effect on the multiple dose pharmacokinetics of omeprazole after a 3 day dosing period.

Ref: Administration of an alginate based gastric reflux suppressant on the bioavailability of omeprazole. P.W. Dettmar, F.C. Hampson, A. Jain, S. Choubey, S.L. Little & T. Baxter. Indian J Med Res 123, April 2006, pp 517-524

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Diagnosis and treatment bleeding peptic ulcers: 2013 WSES position paper

Diagnosis and treatment of bleeding peptic ulcer (Dr. M. Bassi MD)

Introduction

Acute upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency and has a considerable morbidity and mortality. Some but not all time-trend studies have reported a significant decline in incidence of acute UGIB, especially peptic ulcer bleeding (PUB), in recent years. This decline is likely due to a combination of factors, including decreasing prevalence of gastric colonization with *H. pylori*, the use of eradication therapy in patients with ulcer disease, and the increased use of PPI therapy, both in general and in patients using aspirin and NSAIDs in particular.

At the same time, an increasing proportion of patients presenting with UGIB are older and a significant number of patients with UGIB consume NSAIDs and/or antiplatelet therapy to treat other medical comorbidities. Given these factors, UGIB continues to have a considerable impact with respect to patient morbidity and mortality. The mortality rate of UGIB remains high somewhere between 7% and 14%.

The majority of deaths do not directly result from exsanguination, but are related to poorly tolerated blood loss and resultant shock, aspiration, and therapeutic procedures. As such, mortality from UGIB is strongly associated with advanced age and presence of severe comorbidity. The risk of mortality increases with rebleeding, which is thus another major outcome parameter.

The incidence of rebleeding in patients with UGIB shows a wide range from 5% to more than 20%, depending on the aetiology of the bleeding and the timing of endoscopic therapy. There is strong evidence that the risk of rebleeding is highest in the initial period of admission, and a 24-h time frame for endoscopic therapy is internationally recommended as the optimal window of opportunity. Naturally, rebleeding must be prevented whenever possible.

PUB is the most common cause of acute UGIB, accounting for 31%-67% of all cases, followed by erosive disease, varices, oesophagitis, malignancies and Mallory-Weiss tears (Table 1). In the subgroup of patients with PUB, bleeding from duodenal ulcers is slightly more frequent than from gastric ulcers.

Emergency surgery for PUB has continued to decrease; in the UK, the rate of surgery dropped from 8% to 2% between 1993 and 2006. In the same period in the USA, admissions to hospital for peptic ulcer bleeding fell by 28.2%, the use of endoscopic treatment increased by 58.9%, and the rate of emergency surgery for PUB decreased by 21.9%.

Initial assessment, resuscitation and risk-scores

A primary goal of the initial assessment is to determine whether the patient requires urgent intervention (e.g., endoscopic, surgical, transfusion) or can undergo delayed endoscopy or even be discharged to outpatient management. Patients presenting with acute UGIB should be assessed promptly and resuscitated if needed. Volume should be replenished initially with crystalloid solutions. In patients with ongoing blood loss, symptomatic anaemia, or those at increased risk of impaired tissue oxygenation (e.g., patients with chronic heart conditions), blood should be transfused. In haemodynamically stable patients who are not bleeding actively, the threshold of transfusion needs to be defined. International guidelines recommend a policy of transfusion to a haemoglobin concentration of 7 g/dL.

Coagulopathy at presentation is a major adverse prognostic factor. From the UK National Audit, coagulopathy defined by an international normalised ratio (INR) above 1.5 was present in 4% of patients and was associated with a 15% mortality rate. Coagulopathy is also a marker for other comorbidites, such as chronic liver disease. Bleeding in these patients is often more severe, and coagulopathy should be corrected in those with active bleeding. The target INR has not been defined and is established by the patient's indication for anticoagulation. A study showed that mild to moderate anticoagulation (INR 1.3 – 2.7) at endoscopy did not increase the risk of recurrent bleeding compared with an INR of less than. One small cohort study with a historical comparison showed that aggressive resuscitation including correction of coagulation (INR <1.8) led to lower mortality rates.

Table 1 Causes of upper gastrointestinal bleeding

	%
Peptic ulcer	31 – 67
Erosive	7 – 31
Variceal bleeding	4 – 20
Oesophagitis	3 – 12
Mallory-Weiss	4 – 8
Malignancies	2 – 8
Other	2 – 8

Although numerous factors from the patient history, physical examination, and initial tests have been examined for an association with a need for intervention, no single factor is sufficiently predictive of UGIB severity to be used for triage. The most predictive individual factors are a history of malignancy, presentation with hematemesis, signs of hypovolemia including hypotension, tachycardia and shock, and a haemoglobin < 8 g/dL.

Some factors, such as a history of aspirin or NSAIDs use, may not be useful for immediate disposition but are still important to assess for future management (e.g., if PUB were the aetiology of UGIB, then NSAIDs use should be discontinued). Patients who have significant comorbidities may require admission regardless of the severity of the UGIB.

Several scoring systems have been created and/or validated for this purpose, including APACHE II, Forrest classification, Blatchford score, pre-endoscopic Rockall score. Some of these may be cumbersome (APACHE II) or require data not immediately available based on initial clinical assessment (the Rockall Scoring System, for instance, requires endoscopic data) and therefore may be of limited utility in the acute setting.

The Blatchford score and the pre-endoscopic Rockall score have been examined in several studies and may determine the need for urgent endoscopy (Table 2). A Blatchford score > 0 was 99% to 100% sensitive for identifying a severe bleed in 5 studies. The specificity of the Blatchford scoring system is low (4%-44%), but clinically it is more important to be comfortable identifying all severe UGIB at the expense of admitting some patients with minor bleeding episodes. Patients found to have minor bleeding episodes typically may be discharged soon after endoscopy. Use of the Blatchford score may allow early discharge of 16% to 25% of all patients presenting with UGIB.

The use of a nasogastric tube remains controversial; in theory, the presence of bright red blood via nasogastric aspirate suggests active UGIB and should prompt urgent to esophagogastroduodenoscopy (EGD). The absence of blood on nasogastric aspirate, however, does not exclude the presence of a culprit UGIB source.

Pharmacologic therapy prior to endoscopy

Early administration of intravenous PPIs noted a reduction in high-risk stigmata of bleeding (37.2% vs. 46.5%,) and a lower proportion of patients undergoing endoscopic therapy (8.6% vs. 11.7%). The reduction in endoscopic treatment leads to early discharge in some patients. However, the use of proton-pump inhibitors should not replace urgent endoscopy in patients with active bleeding.

A prokinetic drug given before endoscopy helps to empty stomach contents and improves viewing at endoscopy. These drugs are rarely used by endoscopists. The use of these drugs reduces the need for a second endoscopic examination for diagnosis but no significant difference in other clinical outcomes. At present, insufficient evidence exists to support the use of tranexamic acid in acute PUB.

Endoscopic treatment

Endoscopy in patients with PUB is effective and is associated with a reduction in blood transfusion requirements and length of intensive care unit/total hospital stay. The optimal timing for endoscopy in PUB remains under debate.

In appropriate settings, endoscopy can be used to assess the need for inpatient admission. Several studies have demonstrated that hemodynamically stable patients who are evaluated for UGIB with upper endoscopy and subsequently found to have low-risk stigmata for recurrent bleeding can be safely discharged and followed as outpatients. Patients with unstable haemodynamics and active haematemesis should be offered urgent endoscopy with a view to haemostasis. Patients who are stable after initial resuscitation generally undergo endoscopy the next morning. Evidence for the use of early endoscopy (within 24 h) came from cohort studies and their meta-analysis and results in significantly reduction of the hospital stay and improvement of the outcome.

However, although emergency endoscopy should be considered in patients with severe bleeding, very early endoscopy (<12 h) has so far not been shown to provide additional benefit in terms of reduction of rebleeding, surgery and mortality, compared with later endoscopy (within 24 h).

The Forrest classification is used to distinguish endoscopic appearances of bleeding ulcers (Ia spurting active bleeding; Ib oozing active bleeding; IIa visible vessel; IIb adherent clot; IIc flat pigmented spot; III ulcer with a clean base).

In PUB, patients with active bleeding ulcers or a non-bleeding visible vessel in an ulcer bed are at highest risk of re-bleeding and therefore need prompt endoscopic hemostatic therapy.

Table 2 Comparison of Blatchford and Rockall risk scoring systems

Risk factor	Blatchfor Score		Pre endoscopic Rockfall score	
	Parameter `	Score	Parameter `	Score
Age (yr)	-		60-79	1
	-		= 80	2
SBP (mmHg)	100-109	1	<100	2
	90-99	2	-	
	<90	3	-	
BPM	> 100	1	> 100 with SPB = 100	1
Clinical presentation	Melena	1	-	
	Synocpe	2	-	
Comorbidity	Hepatic disease	2	CHF, IHD, major comorbidity	2
	Cardiac failure	2	Renal or liver failure, metastases	3
Blood urea (mg/dL)	18.2-22.3	2	-	
	22.4-27.9	3	-	
	28-69.9	4	-	
	= 70	6	-	
Hemoglobin g/dL	F: 10 – 11.9	1	-	
	M: 10 – 11.9	3	-	
	F/M: < 10	6	-	
			Complete Rockfall score	
Endoscopic diagnosis	-		Non malignant, non Mallory-Weiss	1
	-		Upper GI malignancy	2
Evidence of bleeding	-		Blood, adherent clot, active bleeding	2

M: Male; F: Female; SBP: Systolic blood pressure; CHF: Congestive heart failure; IHD: ischemic hearth disease.

Patients with low-risk stigmata (clean-based ulcer or a pigmented spot in ulcer bed) do not require endoscopic therapy. A clot should be removed in search of an artery and, when it is present, endoscopic treatment should be given, although the management of peptic ulcers with overlying adherent clots that are resistant to removalby irrigation is still controversial.

Endoscopic treatment can be divided into injection (including epinephrine, sclerosants and even normal saline solution), thermal (including monopolar or bipolar cautery and argon plasma coagulation) and mechanical methods (including hemoclips).

Injection of diluted epinephrine alone is inadequate. Cushions of fluid injected into the submucosa compress the artery to stop or slow down bleeding and allow a clear view of the artery. A second modality should be added to induce thrombosis of the artery. If combination treatment had been instituted at index endoscopy, a second look endoscopy would have been unnecessary.

A new endoscopic application is the use of a chemical compound which, when sprayed as nanopowder on active bleeding, can lead to immediate hemostasis.

Early endoscopy (within 24 h) in PUB results in significantly reduction of the hospital stay and improvement of the outcome. Dual endoscopic therapy, rather than monotherapy, led to substantial reductions in rate of recurrent bleeding, surgery and mortality .

Postendoscopic management

PPIs can be administered orally or intravenously depending on the rebleeding risk. Once mucosal healing has been achieved, how long it should last the PPIs use is still controversial. There is a 33% risk of rebleeding in 1 – 2 years. Furthermore, there is a 40%-50% rebleeding risk over the subsequent 10 years.

Randomized prospective trials have demonstrated a benefit to long-term acid-suppression therapy in two settings: chronic NSAID users and H. pylori -infected patients. Testing for *H. pylori* is recommended in all patients with PUB.

High-dose continuous intravenous PPIs is recommended in patients with PUB and high-risk stigmata.

Continued and recurrent bleeding

Despite adequate initial endoscopic therapy, recurrent UGIB can occur in up to 24% of high-risk patients. Large ulcers located in the posterior bulbar duodenum and lesser curvature of stomach can erode into the gastroduodenal or the left gastric artery, respectively, which are predictive of endoscopic treatment failure. These ulcers often occur in elderly patients who present with a major bleed in shock and low initial haemoglobin concentrations.

Patients with massive bleeding who do not respond to endoscopy are often shifted to surgical treatment. Angiographic embolization is an alternative. Surgical procedure of vagotomy/drainage is associated with significantly lower mortality than just with simple local ulcer oversew. Open surgery is recommended when endoscopic treatments failed and there is evidence of ongoing bleeding +/ - hemodynamic instability. The surgeon may not know preoperatively where the bleeding comes from and intraoperative endoscopic guidance may be helpful.

Peptic ulcer bleeding in patients receiving anti-thrombotic therapy

Patients on antiplatelets or anticoagulant therapy with acute UGIB need to be managed on a individual basis. These patients are of course at high risk of thromboembolism because of their underlying cardiovascular illness. However, discontinuation of anti-thrombotic therapy may be necessary to control bleeding or prevent rebleeding.

In a randomised trial of continuous versus discontinued aspirin treatment in patients with PUB and high cardiothrombotic risks, those receiving continuous aspirin had a twofold increased risk of early recurrent bleeding but a tenfold reduced risk of mortality. In patients at low risk of recurrent bleeding, aspirin can be resumed the after-bleeding morning. The antiplatelet effect of aspirin lasts for about 5 days and the risk of early recurrent bleeding is high in the first 3 days; thus, in high-risk cardiovascular patients, it might be reasonable to resume aspirin on fourth day after bleeding to minimise both bleeding and thrombotic risks.

Patients on dual antiplatelet treatment (e.g. aspiring and clopidogrel), especially after recent placement of drug-eluting coronary stents, are at high risk of thrombosis. In patients at low risk of recurrent bleeding, dual antiplatelet treatment should be continued. In those at high risk, cessation of both antiplatelet drugs should be avoided, given the very high risk of stent occlusion. In high-risk patients, after endoscopic control of bleeding, high-dose PPIs infusion and temporarily withholding of clopidogrel is recommended. Early resumption of clopidogrel should be considered in patients who had stent placement within 4 weeks, left main stem disease, and known coronary artery dissection.

Major gastrointestinal bleeding is often associated with anticoagulant therapy. Rapid correction of the coagulopathy is recommended. Intravenous vitamin K will reverse the coagulopathy due to warfarin, but its full effect can take up to 24 hours. Prothrombin complex concentrates rapidly reverse coagulopathy, and this treatment is preferred over fresh frozen plasma, especially in patients with cardiac and renal failure who poorly tolerate fluid overload. Treatment with low-molecular-weight or unfractionated heparin should be considered in almost all cases. However the treatment with unfractionated heparin in the initial stage can be more easily controlled than low molecolar weight heparin.

Reference: Diagnosis and treatment of perforated or bleeding peptic ulcers: 2013 WSES position paper. Salomone Di Saverio, Marco Bassi, Nazareno Smerieri et al. World Journal of Emergency Surgery 2014, 9:45

Congratulations !

The Winners of GI Café Quiz Competition

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Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the second issue, Vol: 7, of GI Café. In this newsletter, we have highlighted the Gastric reflux and Gastric bleeding management. The articles give you some interesting thoughts.

Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

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