Table

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Coulie *et al*,[1] 1989 Belgium	10 healthy adult volunteers exposed to *Anopheles stephensi* mosquitoes in a laboratory.	Double blind randomized crossover trial of cetirizine 10 mg BD *v* placebo.	Effect on pruritus and cutaneous reaction	Reduced pruritus but not intensity or duration of cutaneous reaction	1 volunteer dropped out after a severe skin reaction to cetirizine.
Reunala *et al*,[2] 1991 Finland CA	27 adult volunteers exposed to *Aedes ommunis* mosquitoes in a forest in Southern Finland.	Double blind, placebo-controlled trial of cetirizine 10 mg od.	Effect on pruritus and cutaneous reaction	Cetirizine reduced immediate but not delayed pruritus and cutaneous skin reaction	4 subjects excluded because baseline reactions to bites were too mild.
Reunala *et al*,[3] 1993 Finland	28 adults with previous significant reaction tomosquito bites. Exposed to *Aedes communis* in forests in Finland	Double blind, crossover trial of cetirizine 10 mg od *v* placebo.	Effect on pruritus and cutaneous skin reaction	Cetirizine reduced immediate pruritus and cutaneous reaction	Subjects were patients and hospital employees. Field studies in 2 different forests. No washout period. All subjects allowed to use 1% hydrocortisone cream. Only 18 subjects completed the study.
Reunala 1997 Finland CA	30 volunteers, all sensitive to mosquito bites. Exposure to *Aedes egypti* in the laboratory.	Double blind, crossover of ebastine (10 mg or 20 mg) *v* placebo.	Effect on prutitus and cutaneous reaction	Ebastine reduced immediate pruritus and cutaneous reaction	Only 25 subjects evaluable because of trial violations (2) and possible adverse events (2)… numbers don't add up, I know.
Karppinen *et al*,[4] 2000 Finland	28 children (2–11 years), sensitive to mosquito bites. Exposure to *Aedes egypti* mosquitoes in the laboratory.	Double blind, crossover of 0.3 mg/kg loratadine *v* placebo	Effect on immediate and delayed cutaneous reaction, and immediate pruritus	Loratadine reduced cutaneous reaction and pruritus	25 completed the study. Only 12 evaluated pruritus on a visual analogue scale.
Karppinen *et al*,[5] 2000 Finland	28 mosquito allergic adults exposed to *Aedes communis* in forests in Finland.	Double blind, crossover study of ebastine 20 mg od *v* placebo.	Effect on pruritus and cutaneous reaction	Reduced immediate cutaneous reaction and both immediate and delayed pruritus.	Different forest sites.
Karppinen *et al*,[6] 2002 Finland	29 adults, sensitive to mosquito bites, exposed to *Aedes egypti* in the laboratory.	Double blind, crossover study comparing cetirizine 10 mg, ebastine 10 mg, loratadine 10 mg and placebo.	Effect on pruritus and cutaneous reaction	Cetirizine and ebastine reduced immediate cutaneous reaction and pruritus compared with placebo. Loratadine seemed ineffective	27 subjects completed the study. Dose of loratadine probably too low, given dose used in paediatric study (above).

od, once daily.

in both adults and children. It is not clear whether the same antihistamine will be effective for both adults and children.

1 Coulie P, Wery M, Ghys L, *et al*. Pharmacologic modulation by cetirizine-2 HCl of cutaneous reactions and pruritus in man after experimental mosquito bites. *Skin Pharmacol* 1989;**2**:38–40.
2 Reunala T, Lappalainen P, Brummer-Korvenkontio H, *et al*. Cutaneous reactivity to mosquito bites: effect of cetirizine and development of anti-mosquito antibodies. *Clinical and Experimental Allergy* 1991;**21**:617–622.
3 Reunala T, Brummer-Korvenkontio H, Karppinen A, *et al*. Treatment of mosquito bites with cetirizine. *Clinical and Experimental Allergy* 1993;**23**:72–75.
4 Reunala T, Brummer-Korvenkontio H, Petman L, *et al*. Effect of ebastine on mosquito bites. *Acta Derm Venereol* 1997;**77**:315–316.
5 Karppinen A, Kautiainen H, Reunala T, *et al*. Loratadine in the treatment of mosquito-bite-sensitive children. *Allergy* 2000;**55**:668–671.
6 Karppinen A, Petman L, Jekunen A, *et al*. Treatment of mosquito bites with ebastine: A field trial. *Acta Derm Venereol* 2000;**80**:114–116.
7 Karppinen A, Kautiainen H, Petman L, *et al*. Comparison of cetirizine, ebastine and loratadine in the treatment of immediate mosquito-bite allergy. *Allergy* 2002;**57**:534–537.

The use of vasoconstrictor therapy in non-variceal upper GI bleeds

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A short cut review was carried out to establish whether vasoconstrictor therapy is indicated for patients who present with an acute upper gastrointestinal (GI) bleed without known oesophageal varices. In total, 1123 citations were reviewed, of which 16 answered the three part question. The clinical bottom line is that somatostatin (SST) should be considered in unwell patients who are likely to be bleeding secondary to peptic ulcer disease (PUD) until definitive endoscopy, or in situations when endoscopy is contra-indicated or unavailable. There is no definitive evidence for the length of time treatment should continue.

Three part question

[In patients with acute severe non variceal upper GI bleed] is [the use of vasoconstrictor therapy] indicated [to control bleeding and prevent re-bleeding].

Clinical scenario

A 65 year old man presents to the ED with a large, fresh upper GI bleed. He has a history of non-steroidal anti-inflammatory drug (NSAID) use and complains of increasing indigestion over the last few months. On examination, he has no stigmata of chronic liver disease and is unwell with blood pressure (BP) of 80 mmHg systolic and tachycardia of 140mmHg. In view of his history and lack of positive examination findings you feel that the most likely diagnosis is a bleeding peptic ulcer. You wonder if there is any evidence to support the use of vasoconstrictor therapy in non-variceal upper GI bleeds.

Search strategy

Medline (Ovid interface)1966–2006: {upper gi bleed.mp. OR exp Gastrointestinal Hemorrhage/or exp Hematemesis/OR haematemesis.mp. OR hematemesis.mp. OR gastrointestinal adj5 haemorrhage.af. OR gastrointestinal adj5 hemorrha-

Table

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Imperiale *et al*,[1] 1997 USA	1829 patients from 14 randomised clinical trials comparing SST or octreotide with H2 blockers or placebo in patients with clinical or endoscopic evidence of acute nonvariceal upper GI haemorrhage. 7 trials placebo controlled, 7 used cimetidine, 5 used ranidine. 8 trials blinded	Meta-analysis of 14 trials;database search of English language articles between 1966 and 1996 and the bibliographies of all related articles and textbook chapters. Medline Jan 66–Oct 96, Embase 1980–1996	Continued bleed or rebleed (all trials) Surgery (all trials) Continued bleed or rebleed (SST only) Continued bleed or rebleed (octreotide only) Continued bleeding (SST only) Surgery (SST only) Investigator blinded trials: Continued bleeding or rebleed Surgery For PU bleeding alone, continued/rebleed Non peptic ulcer bleeding, continued/rebleed	RR 0.53 (95% CI 0.43 to 0.63) NNT5 RR 0.71 (CI 0.61 to 0.81) NNT8 RR 0.50 (CI 0.39 to 0.60) NNT5 RR 0.72 (CI 0.35 to 1.08) NS RR 0.41 (CI 0.29 to 0.53) NNT4 RR 0.70 (CI 0.58 to 0.82) NNT7 RR 0.73 (CI 0.64 to 0.81) NNT11 RR 0.94 (CI 0.87 to 1.001) RR 0.48 (CI 0.39 to 0.59) NNT 4 RR 0.62 (CI 0.39 to 1.002)	Very heterogeneous studies re protocols and doses of drugs, outcome measures, interventions and study groups (some high risk only, some excluded high risk. proportion of patients with active bleeding ranged from 13–100%)). ?Publication bias; though calculations show would need 18 trials showing no difference for p>0.05, are h2 blockers equivalent to placebo? What is the ideal treatment duration?
Archimandritis *et al*,[2] 2000 Greece	84 patients over a 12 month period, scoped within the first 24 hours. Randomised to ranitidine and octreotide (50 mg IV three times daily and 100 µg S/C tds)(40) or ranitidine (50 mg IV tds) alone (44).	Prospective RCT; not blinded	No. of units tx – ranitidine Ranitidine/octreotide Days in hospital: ranitidine Ranitidine/octreotide Txd patients: ranitidine Ranitidine/octreotide Emergency op: ranitidine Ranitidine/octreotide	1.07 ± 0.24 1.7 ± 0.37 p = 0.16 (NS) 8.39 ± 0.47 9.20 ± 0.53 p = 0.25 (NS) 23/44 21/40 p = 1.0 (NS) 3 3 p = 1.0 (NS)	Not blind. Small numbers. S/C octreotide and ?wrong dose
Saruc *et al*,[3]*l* 2003 Turkey	21 patients with bleeding peptic ulcer-endoscoped within 6 hours. Given SST 250 µg/hr for 72 hrs after bolus 250.Each patient had SMA-V, SMA-PI, PV-F and RA-RI measured by doppler on day 1 of infusion infusion and 6 hours post-infusion	Observational lab trial -not blind	PV-F-during infusion PV-F-post infusion SMA-V during infusion SMA-V post infusion SMA-PI during infusion SMA-PI post infusion Correlation between PV-F and risk of rebleed Correlation between SMA-V and risk of rebleed No change in RA-RI	33.7 ± 12.7 cm3/s 56.3 ± 16.0 p = 0.001 39.7 ± 13.1 64.4 ± 15.1p = 0.01 2.0 ± 0.8 2.8 ± 0.8 p = 0.02 r = 0.55, p = 0.03 (r = 0.2 is correlation) r = 0.22, p-0.22	Laboratory trial. Not blind. Small numbers. High no of exclusions including NSAID use. ?Correlation between large vessel flow and clinical picture. ?Influence of mucosal bleeding
Avgerinos *et al*,[3] 2005 Greece	43 patients with malaena/haematemesis with endoscopic signs of stages 2c and 3 Forrest classification. Randomised to SST (15), pantoprazole (14) or placebo (14) and then had gastric pH monitoring for 24 hrs	Prospective RCT (placebo controlled)-double blind	Mean gastric pH -SST PAN Placebo	1.94 ± 0.18 to 6.13 ± 0.37 p<0.0001 1.93 ± 0.16 to 5.65 ± 0.37 p<0.0001 1.86 ± 0.12 to 2.10 ± 0.15 p = 0.0917	pH study only with no correlation to actual risk of rebleed or need for surgical intervention according to power calculations, study sample not large enough; however, study stopped as SST appeared superior to placebo high no of patients excluded from trial (143).

IV, intravenous, S/C, subcutaneous; tds, three times daily, NS, non-significant; GI, gastrointestinal, PU, peptic ulcer; SST, somatostatin; SMA-V superior mesenteric artery velocity; SMA-PI, SMA pulsatility index; PV-F, portal venous volume flow; RA-RI, renal artery resistance index.

ge.af. OR gi adj5 bleed.af. OR peptic ulcer disease.mp. OR exp peptic ulcer/OR gastric ulcer.af. OR duodenal ulcer.af.} AND {terlipressin.mp. OR vasopressin.mp. OR exp vasopressin/OR antidiuretic hormone.mp. OR adh.mp. OR exp somatostatin/OR somatostatin.mp OR somatostatin analogue.mp. OR octreotide.mp. OR exp octreotide/OR glypressin.mp}. Limit to human and English language.

Search outcome

In total, 1123 paperswere found. Of these, 16 randomised clinical trials, 1 laboratory study, 1 review article and 1 meta-analysis found that were relevant to the three part question.

Comment(s)

In approximately 80% of non-variceal upper GI bleeds, bleeding stops spontaneously. However, the remaining 20% will require treatment for either continued bleeding or rebleed.(the majority will survive the primary bleed). This high risk group mainly comprise those patients with continued oozing at endoscopy or non-bleeding visible vessel. Despite the use of diagnostic and therapeutic endoscopy and improved medical treatment over the last 40 years, the mortality for patients with non variceal UGI bleeds remains at 6–7%. Hence, the search for other effective medical interventions, such as the use of vasoconstrictors.

SST has a number of effects on the GI tract including inhibition of gastric acid secretion, pancreatic secretion and biliary secretion. It also reduces gatsric mucosal blood flow, gastric perfusion and stimulates mucus production. Octreotide has a similar secretory effect but it is unknown whether it elicits the same effect on the mucosa or blood flow.

The meta-analysis covering 14 RCTs show good evidence for the use of SST in acutely bleeding peptic ulcer to reduce the risk of continued bleeding, and a trend for reducing the need for surgery. The pH study and doppler studies theoretically support its use, as SST is shown to increase gastric pH (and thus allow optimum platelet function and decrease fibrinolysis) and decrease arterial blood flow, though with no date re clinical correlation.

The two octreotide studies included in the meta-analysis have completely different conclusions—the blinded trial showing no effect on outcome, the non-blinded trial concluded that octreotide stopped PU bleed, decreased Tx requirements and need for surgery. The further non blinded RCT by Archimandritis concluded that octreotide is not superior to ranitidine.

There were no published studies on the use of terlipressin.

In conclusion, there is an evidence base for the use of SST in severe, acute, non variceal peptic ulcer bleeding, but not for other vasoconstricors at present.

What is needed is a large study looking at the efficacy of SST in specific patient groups, defined by source of, and severity of bleeding (ie active/non bleeding visible vessel).

► CLINICAL BOTTOM LINE

SST should be considered in unwell patients who are likely to be bleeding secondary to PUD until definitive endoscopy, or in situations when endoscopy is contraindicated or unavailable. There is no definitive evidence for the length of time treatment should continue.

1 Imperiale *et al* Somatostatin or Octreotide compared with H2 antagonists and placebo in the management of acute non variceal upper. GI haemorrhage *Annals of internal medicine* 1997:**127**(12):1062–71.
2 Archimandritis at al Ranitidine versus ranitidine plus octreotide in the treatment of acute non-variceal upper gastrointestinal bleeding:A prospective randomised study. *Current Medical and Research Opinion* 2000;**16**(No3):178–183.
3 Saruc *et al* Somatostatin infusion and hemodynamic changes in patients with non-variceal upper gastrointestinal bleeding: a pilot study. *Med Sci Monit* 2003;**9**(7):184–87.
4 Avgerinos *et al* Somatostatin inhibits gastric acid secretion more effectively than pantoprazole in patients with peptic ulcer bleeding:A prospective randomised, placebo controlled trial. *Scandinavian Journal of Gastroenterology* 2005;**40**:515–522.

Water soluble, small bowel follow through for adhesive small bowel obstruction

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A short cut review was carried out to establish whether water soluble contrast small bowel follow through studies are useful in the management of patients with suspected adhesive small bowel obstruction (ASBO). In total, 152 papers were found using the reported search, of which 21 represented the best evidence to answer the clinical question. The clinical bottom line is that administration of oral contrast medium in patients with ASBO reduces the need for operation, hastens resolution of obstruction, and reduces length of hospital stay. Oral water soluble contrast follow through studies should be performed in patients presenting with ASBO who are not obvious candidates for immediate operative treatment.

Clinical scenario

A 65 year old woman is brought into the emergency department following a 3 day history of nausea and vomiting, abdominal distension, and absolute constipation. Her vital signs are stable, and his abdomen is distended but not tender. A lower midline laparotomy scar from a previous hysterectomy is noted. A plain abdominal radiograph shows distended loops of small bowel with a paucity of air in the colon. A clinical diagnosis of ASBO is made. You wonder whether a water soluble contrast small bowel follow through (SBFT) study would be useful in the management of a patient with presumptive ASBO.

Three part question

In an [adult patient with previous abdominal surgery presenting with small bowel obstruction] is [water soluble contrast small bowel follow through] useful in [reducing need for operation, time to resolution, length of hospital stay and predicting those patients who will require operative treatment].

Search strategy

Medline 1950 to March 2006 using the Dialog Datastar interface: [small ADJ bowel ADJ obstruction] AND [water ADJ soluble ADJ contrast] OR [Contrast−Media#.DE. OR gastrografin] AND LG = EN

Outcome

In total,152 papers were found, of which 21 were relevant to the topic.

ASBO, adhesive small bowel obstruction, NS, not significant. Level of evidence: level 1 denotes that a recent well-performed systematic review was considered or a study of high quality is available.

Comment(s)

Published literature strongly supports the use of water soluble contrast as a predictive test for non-operative resolution of adhesive small bowel obstruction. The evidence supports that amidotrizoate hastens resolution of small bowel obstruction and reduce length of hospital stay.

► CLINICAL BOTTOM LINE

Administration of oral contrast medium in patients with ASBO reduces the need for operation, hastens resolution of obstruction and reduces length of hospital stay. Oral water soluble contrast follow through studies should be performed in patients presenting with ASBO who are not obvious candidates for immediate operative treatment.

1 Kapoor S, Jain G, Sewkani A, *et al*. Prospective evaluation of oral gastrografin in postoperative small bowel obstruction. *J Surg Res* 2006;**131**:256–60.
2 Abbas S, Bissett IP, Parry BR. Oral water soluble contrast for the management of adhesive small bowel obstruction. *Cochrane Database Syst Rev* 2005: CD004651.
3 Burge J, Abbas SM, Roadley G, *et al*. Randomized controlled trial of Gastrografin in adhesive small bowel obstruction. *ANZ J Surg* 2005;**75**: 672–4.
4 Choi HK, Law WL, Ho JW, *et al*. Value of gastrografin in adhesive small bowel obstruction after unsuccessful conservative treatment: a prospective evaluation. *World J Gastroenterol* 2005;**11**:3742–5.
5 Yagci G, Kaymakcioglu N, Can MF, *et al*. Comparison of Urografin versus standard therapy in postoperative small bowel obstruction. *J Invest Surg* 2005;**18**:315–20.