How should continuous infusions of branded proton pump inhibitors be given for acute upper gastrointestinal bleeding?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Date prepared: 18th September 2012

Background

Acute upper gastrointestinal bleeding is associated with significant morbidity and mortality. In high-risk patients, once the initial episode of bleeding has been controlled by endoscopic therapy, the goal is to prevent rebleeding and associated complications. The rebleeding rate after initial endoscopic haemostasis of upper gastrointestinal ulcers may be as high as 10% to 25% (1).

Acid and pepsin impair the haemostatic process of ulcers and non-variceal upper gastrointestinal lesions (1). It has been suggested that increasing and maintaining intragastric pH to ≥ 6.0 may decrease the risk of rebleeding by increasing clot stability (2).

Intravenous proton pump inhibitors (PPIs) have been shown to provide potent and long lasting acid suppression, without the development of tolerance (1).

Answer

In the UK, intravenous formulations of omeprazole, pantoprazole and esomeprazole are currently available (3). Omeprazole and pantoprazole are not licensed to be given by continuous infusion (4,5). Intravenous esomeprazole is licensed for the prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers (6).

Dose

The National Institute for Health and Clinical Excellence (NICE) recommends that proton pump inhibitors should be offered to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy (7). However, the route of administration and dosage are not specified.

Current guidance from the Scottish Intercollegiate Guidelines Network (SIGN) recommends that “high-dose intravenous PPI therapy (e.g. omeprazole or pantoprazole 80mg bolus followed by 8mg/hour infusion for 72 hours) should be used in patients with major peptic ulcer bleeding (active bleeding or non-bleeding visible vessel) following endoscopic haemostatic therapy” (8). The British Society of Gastroenterology states that it has decided to commend the SIGN document and adopt it as a standard of care (9). International Consensus Recommendations advise the same regimen to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy (10).

Administration

The administration details and stability data given below refer to the branded products stated.

Omeprazole is available as Losec® intravenous infusion and Losec® IV injection, both as 40mg vials. The two preparations have different excipients and due to a lack of stability data the injection is not interchangeable with the infusion. Losec® IV injection must be given only as an intravenous injection and it must not be added to infusion solutions (11). To avoid confusing the two varieties of the same injectable, the Losec® intravenous infusion preparation should be used for this indication.
The exact administration details for the initial IV omeprazole 80mg dose followed by an 8mg/hour infusion are not always stated in the published clinical trials. However, the omeprazole monograph in the BNF states that omeprazole should be given as an initial intravenous infusion of 80mg over 40–60 minutes (3). After the initial 80mg dose has been given, one 40mg intravenous infusion vial should be reconstituted with approximately 5ml of sodium chloride 0.9% or glucose 5%, immediately diluted to 100ml using the same infusion fluid (4) and then administered at a rate of 8mg/hour (3), i.e. over 5 hours. This can then be repeated with a new vial each time until the 72 hour period is completed. The manufacturer has information to show that the product is chemically and physically stable in sodium chloride 0.9% for 12 hours and in glucose 5% for 6 hours at 25°C (4), and a published study shows chemical stability in both infusion fluids for up to 48 hours (at 22°C) (12). Despite this the vial does not contain a preservative and the manufacturer advises from a microbiological point of view that the reconstituted solution should be used immediately unless it has been reconstituted under controlled and validated aseptic conditions (4).

Pantoprazole is available as Protium® injection in a 40mg vial. Again, an 80mg IV dose is given initially, followed by a continuous infusion. For infusion one vial should be reconstituted with 10ml sodium chloride 0.9% and then further diluted with 100ml sodium chloride 0.9% or glucose 5%. The SPC states that the reconstituted solution is chemically and physically stable for 12 hours at 25°C (5), yet a published study again shows chemical stability for up to 48 hours (at 22°C) (12). However, note that the SPC also states that, from a microbiological point of view, the reconstituted product should be used immediately. If not, in-use storage times and conditions are the responsibility of the user (5).

In a pilot study, each 40mg pantoprazole vial was reconstituted with 10ml sodium chloride 0.9% and an initial bolus injection of 80mg (two reconstituted vials, total 20ml) was given intravenously over 2 minutes. Following this initial dose, three reconstituted vials of 40mg pantoprazole in 30ml sodium chloride 0.9% was infused, protected from direct light, at a constant rate of 8mg/hour and a fresh solution prepared every 12 hours until the end of the infusion (72 hours) (13). No stability data were given and this concentration of pantoprazole infusion is not licensed by the manufacturer.

Esomeprazole is available as Nexium® IV 40mg powder for solution for injection/infusion. Following therapeutic endoscopy, 80mg should be administered intravenously over 30 minutes, followed by a continuous intravenous infusion of 8mg/hour given over 71.5 hours (total infusion time is therefore 72 hours). A solution for infusion of 80mg is prepared by dissolving the contents of two vials of esomeprazole 40mg in up to 100ml of 0.9% sodium chloride for intravenous use. After reconstitution, chemical and physical in-use stability has been demonstrated for 12 hours at 30°C. From a microbiological point of view, the product should be used immediately (6).

Summary

- Current guidance recommends that high-dose intravenous PPI therapy (80mg bolus followed by 8mg/hour infusion for 72 hours) should be used in patients with major peptic ulcer bleeding following endoscopic haemostatic therapy (8,9,10).

- Omeprazole and pantoprazole are not licensed to be given by continuous intravenous infusion (4,5) and use in this way is therefore the responsibility of the prescribing physician. Intravenous esomeprazole is licensed for the prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers (6).

- After administration of the initial 80mg dose, the continuous infusion can be prepared by reconstituting a 40mg vial of either omeprazole (Losec® infusion) or pantoprazole (Protium®) and further diluting in 100ml of sodium chloride 0.9% or glucose 5%. This can be given at a rate of 8mg/hour (i.e. over 5 hours), and repeated with a fresh vial after that time. Depending on the host organisation’s attitude to microbiological stability, infusions could be made up and run over 24-48 hours if necessary since omeprazole (Losec®) and pantoprazole (Protium®) at a concentration of 400 microgram/ml are chemically stable in sodium chloride 0.9% or glucose 5% for this period (12).
After administration of the initial intravenous dose of 80mg esomeprazole, the contents of two 40mg vials of esomeprazole are dissolved in up to 100ml of 0.9% sodium chloride and given at a rate of 8mg/hour (i.e. over 10 hours). This is repeated with fresh vials after that time (6).

**Limitations**
- This Q&A has concentrated on the technical details of how intravenous PPIs are given and not the evidence to support their use and effective dose for the indications described, their relative efficacy, nor their safety profiles.
- The administration details and stability data included in this Q&A refer to the branded products stated.
- Cost-effectiveness studies, the use of IV PPIs prior to endoscopy and studies in children have not been considered.
- Only the use of IV PPIs for the management of non-variceal upper gastrointestinal bleeding has been addressed.

**References**

From the NHS Evidence website [www.evidence.nhs.uk](http://www.evidence.nhs.uk)
Quality Assurance

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Date Prepared
18th September 2012

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Date of check
17th October 2012

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