

# Intravenous administration of proton pump inhibitors in upper gastrointestinal bleeding

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**TITLE** Intravenous proton pump inhibition utilization and prescribing patterns escalation: a comparison between early and current trends in use

Published online November 2008

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**JOURNAL** *Gastrointest Endosc* 2008 Aug 19 [epub ahead of print].

**DECLARATION OF INTERESTS** No conflict of interests declared.

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## SUMMARY

This paper, from a tertiary care university hospital in Vancouver, retrospectively examines trends in the use and prescribing of IV pantoprazole in two study periods: (a) when pantoprazole was restricted to the gastroenterology service (November 1999–June 2001) and (b) when it became unrestricted (June 2003–May 2004). The authors reviewed utilisation patterns to determine whether use of the medication had increased, which medical service was responsible for any increased utilisation, if the indications had expanded and whether this was associated with better patient outcomes.

Intravenous proton pump inhibitor (IV PPI) usage was clearly increased, with 516 patients in period (b) receiving IV PPI on 613 occasions, compared with only 217 patients on 218 occasions in period (a). The indications had also expanded, although not obviously in an evidence-based manner; in group (a) 93.12% of 217 patients received IV PPI for non-variceal upper gastrointestinal bleeding (NVUGIB), while in group (b) only 56.12% of 516 patients ( $P < 0.0001$ ) received IV PPI for NVUGIB. Almost one third of patients in group (b) received IV PPI for other reasons, namely nil by mouth status (18%) and abdominal pain (13%). More than 70% of patients in group (a) underwent upper endoscopy compared with only 45% patients in group (b); in group (a) 54.9% were already on IV PPI at the time of endoscopy compared with almost everybody in group (b) (92%,  $P < 0.0001$ ).

It was of particular interest that fewer patients in group (b) had high risk for bleeding lesions at endoscopy, translating to less therapeutic intervention. In a direct comparison of confirmed cases of NVUGIB between the two study periods, there was a similar rate of surgical intervention but a significant reduction in rebleeding (from 16% to 9%) and death (from 34% to 16%) in group (b).

With regards to prescription patterns, in period (a) when the drug could only be given by a gastroenterologist, only 3% of prescriptions came from emergency physicians, while in period (b) more than 11% came from emergency physicians and the prescription rates from non-gastroenterologists doubled.

The authors concluded that IV PPI usage before endoscopy has escalated in their hospital, and fewer patients had high-risk endoscopic stigmata of bleeding on endoscopy. At the same time, they accepted that the expansion of the medication's usage was well beyond any evidence available for its benefit.

## OPINION

Intravenous PPI use following endoscopy for NVUGIB<sup>1</sup> represents the most important recent development in the non-surgical management of patients with this condition since the advent of endoscopic adrenaline injection. Although this treatment has not been shown to have an impact on mortality, it reduces the risk of rebleeding and the need for surgery.<sup>2</sup>

More recently, data have emerged on the pre-emptive use of IV PPI prior to endoscopy, which has been associated with the accelerated resolution of stigmata of recent bleeding and the reduced need for endoscopic therapy.<sup>3</sup> Accordingly, there has been a tendency for pre-endoscopic use of IV PPI, which has raised questions regarding inappropriate use of this expensive medication, in particular when there is uncertainty about the diagnosis of upper gastrointestinal bleeding.

This paper comes from a centre with an early belief that IV PPI use prior to endoscopy is of benefit.<sup>3</sup> This is reflected in the present study by the fact that even in the earlier study period (1999–2001), more than 50% of the NVUGIB patients in Vancouver were receiving IV PPI

prior to endoscopy following approval from a gastroenterologist. At this time, the one major prospective randomised trial available recommended IV PPI use only after endoscopy.<sup>1</sup>

A publication in 2005<sup>4</sup> by some of the authors of the present paper, auditing the use of IV PPI in several Canadian hospitals, found that the pre-endoscopic use of IV PPI down-staged lesions at endoscopy, although there was no impact on mortality, rebleeding or surgical intervention. Furthermore, the same researchers found that pre-endoscopic IV PPI prescription might have been beneficial in preventing a number of complex and expensive therapeutic interventions in high-risk bleeders.<sup>5</sup> In Canada, therefore, the widespread use of IV pantoprazole had been approved before the US, and as such there is a significant amount of data accumulated on the pre-endoscopic use of IV PPI, perhaps more than anywhere else in the world.

In the UK, most gastroenterologists would accept that IV PPI post therapeutic endoscopy is of definite value, and this has been shown in a meta-analysis by Leontiadis et al.<sup>2</sup> and, more recently, in a systematic review commissioned by *Health and Technology Assessment*.<sup>6</sup> It should therefore be standard practice to administer IV PPI treatment post therapeutic endoscopy as an 80-mg IV bolus dose of omeprazole or pantoprazole (or other IV PPI equivalent), followed by 8 mg/h IV infusion for 72 hours; such a regime reduces rebleeding and surgical intervention. The scientific basis of such treatment is that clot stabilisation is best achieved at a gastric pH greater than 6.<sup>7</sup>

There is still scepticism, however, regarding the value of IV PPI administration, in particular IV infusion, prior to endoscopy. Andrews et al.,<sup>4</sup> despite finding a reduction in the proportion of patients with stigmata of recent haemorrhage at index endoscopy, failed to demonstrate any reduction in mortality, rebleeding or the need for surgery.

Lau et al.<sup>3</sup> published the first large prospective randomised control study of 80 mg IV bolus of omeprazole followed

by 8 mg/h IV infusion until next-day endoscopy versus placebo, and produced similar results. There were no significant differences between the omeprazole and the placebo group in the amount of blood transfused and in the number of patients who had recurrent bleeding, who underwent emergency surgery or who died within 30 days. The hospital stay, however, was reduced in the omeprazole group. The study was limited by the fact that patients on regular aspirin prior to bleeding were excluded.

This study by Law et al., which is in effect an audit of a practice established despite the lack of evidence for improved outcome, shows an impressive reduction in blood transfusion requirements, rebleeding and death when IV PPI was administered early and almost routinely prior to endoscopy. Being a retrospective study, there are concerns about selection bias, although the authors reassure us that by including all IV PPI prescriptions this was not a limitation. It is also unclear whether there have been differences in the timing of endoscopy and whether the patient cohort in the two study periods had similar co-morbidities, beyond the severity of the bleed. The quoted mortalities of 34% in the earlier and 15.9% in the later period are very high and reflect a group of very sick patients.

The Canadian experience, however, should not be ignored. Perhaps in selected high-risk patients or when endoscopy is not possible or likely to be delayed, early IV PPI administration pre endoscopy may benefit patients. Such decisions should be reserved for the specialist gastroenterologist, while more data from prospective randomised control trials become available. There is also the theoretical benefit that IV PPI use prior to endoscopy may improve the endoscopic appearance of a bleeding ulcer and facilitate more effective endoscopic therapy, although no data to support this are available.

The potential for inappropriate use of this expensive treatment has been demonstrated in the present study. Nil by mouth or abdominal pain are not indications for IV PPI use, in particular with the availability of oral-dispersible proton pump inhibitors.

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