Description of prescribing practices in patients with upper gastrointestinal bleeding receiving intravenous proton pump inhibitors: A multicentre evaluation

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BACKGROUND: Intravenous forms of proton pump inhibitors (IV PPI) are routinely used for patients with acute upper gastrointestinal bleeding, but a significant concern for their inappropriate use has been suggested.

PATIENTS AND METHODS: All consecutive patients who received IV PPI (pantoprazole) over 20 months in six Canadian hospitals were reviewed. Prescribing practices, endoscopic findings and outcomes were recorded.

RESULTS: A total of 854 patients received IV PPI. Over 90% of patients were given IV PPI for treatment of known or suspected active upper gastrointestinal bleeding. Most patients (69%) underwent upper endoscopy, and 58% of these patients had peptic ulcer disease (PUD). The majority of patients who had endoscopy (57%) had IV PPI administered in advance of the procedure. Of the 334 patients who had IV PPI given in advance, 46 (13.8%) were found to have high risk bleeding PUD stigmata at endoscopy. The remaining 288 patients (86.2%) with advance IV PPI had low-risk PUD lesions or non-PUD lesions; IV PPI was continued after endoscopy in 164 (56.9%) of these patients.

CONCLUSIONS: IV PPI is often used before endoscopy in suspected upper gastrointestinal bleed and maintained, regardless of endoscopic findings, after the endoscopy in many Canadian centres. Further study is required to support these clinical practices.

Key Words: *Acid suppression; Gastrointestinal bleeding; Peptic ulcer disease; Proton pump inhibition*

La description des pratiques de prescription aux patients présentant une hémorragie des voies gastro-intestinales supérieures qui prennent des inhibiteurs de la pompe à protons par intraveineuse : Une évaluation multicentrique

HISTORIQUE : Les inhibiteurs de la pompe à protons par intraveineuse (IPP IV) sont utilisés systématiquement pour les patients souffrant d'une hémorragie aiguë des voies gastro-intestinales supérieures, mais on s'inquiète énormément du risque d'en faire un usage inopportun.

PATIENTS ET MÉTHODOLOGIE : Les dossiers de tous les patients consécutifs qui ont reçu des IPP IV (pantoprazole) sur une période de 20 mois dans six hôpitaux canadiens ont été analysés. Les pratiques de prescription, les observations endoscopiques et les issues ont été prises en note.

RÉSULTATS : Au total, 854 patients ont reçu des IPP IV. Plus de 90 % des patients ont reçu des IPP IV pour traiter une hémorragie active connue ou présumée des voies gastro-intestinales supérieures. La plupart des patients (60 %) avaient subi une endoscopie supérieure, et 58 % de ces patients souffraient d'un ulcère gastroduodénal. Avant l'intervention, des IPP IV ont été administrés à la majorité des patients qui devaient subir une endoscopie (57 %) avant l'intervention. Des 334 patients qui avaient ainsi reçu des IPP IV, 46 (13,8 %) ont présenté des stigmates d'ulcère gastroduodénal à haut risque d'hémorragie à l'endoscopie. Les 288 autres patients (86,2 %) ayant reçu des IPP IV à l'avance souffraient de lésions d'ulcère gastroduodénal à faible risque ou non reliées à un ulcère gastroduodénal. Les IPP IV étaient maintenus chez 164 (56,9 %) de ces patients après l'endoscopie.

CONCLUSIONS : Les IPP IV sont souvent utilisés avant l'endoscopie en cas d'hémorragie présumée des voies gastro-intestinales supérieures, puis maintenues après l'endoscopie dans de nombreux centres canadiens, quels que soient les résultats de l'endoscopie. Des études plus approfondies s'imposent pour étayer ces pratiques cliniques.

The advent of proton pump inhibitors (PPI) has greatly improved the treatment of acid-related disorders, but their role in the setting of acute upper gastrointestinal (UGI) hemorrhage from peptic ulcer disease (PUD) is only recently coming into focus (1-7). Prospective, randomized controlled trials have demonstrated efficacy in decreasing rebleeding from high-risk peptic ulcers (defined as active bleeding or presence of a nonbleeding visible vessel) after endoscopic therapy (6).

The optimal dose of intravenous (IV) PPI has been extrapolated from pH studies which suggest that a pH greater than 6

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is critical in stabilizing clots (8-10). This is consistently achieved with a bolus of 80 mg followed by a continuous infusion of IV PPI, as used in key clinical studies (11). The optimal timing of administration of IV PPI is not known. In most studies, IV PPI was administered after endoscopic assessment with or without endoscopic therapy. Recently, cost analysis has suggested that IV PPI may be cost-effective if given before the endoscopic examination (12). Additionally, other Canadian National Registry studies have suggested that other patient groups may benefit from IV PPI. In the Registry of Upper Gastrointestinal Bleeding and Endoscopy (RUGBE), patients with low-risk PUD lesions and those with other nonvariceal bleeding lesions also appeared to benefit from IV PPI, thereby suggesting that more liberal use of these drugs may be warranted (13).

Despite the fact that studies have supported the use of acid suppression for UGI bleeding from PUD, approval for the use of IV PPI in this context has not been obtained by regulatory authorities in Canada and the United States. Very few data exist on the use of IV PPI in the North American context. We therefore reviewed a large cohort of patients treated with IV PPI in a variety of medical centres to gain insight into how physicians are using IV PPI, particularly in the setting of PUD.

METHODS

All consecutive patients who received IV pantoprazole from November 1999 to June 2001 (20 months) in six hospitals in the metropolitan Vancouver, British Columbia area were identified from hospital pharmacy databases and reviewed retrospectively. Three of the hospitals were academic teaching hospitals and three were nonacademic secondary or tertiary care hospitals.

IV formulations of a PPI (specifically pantoprazole) were approved in Canada in September 1999. They were placed on the formulary in the province of participating hospitals shortly thereafter (November 1999), and their use was unrestricted. Other IV PPIs were not used at the hospitals evaluated during the study period.

Data were abstracted from hospital records using a standardized information template. The timing, dose and duration of administration of IV PPI, indications for use, demographic data (including comorbidities and risk factors for PUD), baseline hemoglobin and systolic blood pressure, ordering physician, timing of endoscopy, endoscopic findings and intervention, and outcomes were recorded.

Definitions

High-risk peptic ulcer stigmata were defined as active bleeding (oozing or spurting) or the presence of a nonbleeding visible vessel. If patients had more than one endoscopy per admission, only the results from the first endoscopy were recorded.

Rebleeding was defined as a postresuscitation drop in hemoglobin of at least 20 g/L, a sudden drop in systolic blood pressure of more than 20 mmHg unexplained by medications, or evidence of new hematemesis or melena stool. Any rebleeding within 30 days of the initial bleed was included, unless otherwise specified.

Surgery was defined as any laparotomy undertaken for control of UGI bleeding or perforation from any source after identification and/or resuscitation of initial UGI bleed.

Intensive care unit (ICU) admission was defined as admission to an ICU for monitoring or hemodynamic instability as a direct result of UGI hemorrhage. Patients who developed GI bleeding while admitted to an ICU for other reasons were excluded. Typically, in the hospitals included in the study, patients with routine UGI bleeding are not admitted to the ICU. Patients usually require multiorgan system failure to gain access to an ICU.

Death was defined as death from any cause within 30 days of initial UGI bleeding.

Patients who had ceased to have acute medical issues but who were then waitlisted for extended care facilities on the same admission were deemed to be discharged on the date they were waitlisted for an alternate level of care.

Statistical analysis

Differences between the means of continuous variables were assessed using Student's *t* test or one-way ANOVA. Ordinal variables were compared using the Mann-Whitney U test. Differences in group proportions were analyzed with the Pearson χ^2 test, or the Fisher's exact test if sample sizes were small. Two-tailed tests of significance at the $P<0.05$ level were used to determine statistical significance.

RESULTS

Population

A total of 854 patients in six hospitals were found to have received IV pantoprazole (Table 1). The predominantly male population (62%) had a mean age of 63 years. Fifty-nine per cent were either admitted for bleeding or had bleeding within the first 48 h of admission.

The median length of stay was 10 days. The comorbidity of the patients was high, with 53% of the patients having concomitant comorbidities affecting two or more organ systems. Only 132 patients (15.5%) had no other comorbidity. Patients in the academic tertiary centres had significantly higher comorbidity than patients in the community hospitals (2.0 versus 1.0, $P<0.001$).

Risk factors for PUD bleeding

A significant proportion of patients had prior risk factors for the development of PUD, including a previous history of PUD (21.7%), current or recent use of nonsteroidal anti-inflammatory drugs (25.3%), or admission to an ICU (12.8%). Over 20% of the patients had more than one risk factor.

Indications

Over 90% of patients were given IV PPI for treatment of known or suspected active UGI bleeding (Table 1). The remainder of the patients received IV PPI for other reasons (ie, bleeding prophylaxis or treatment of gastroesophageal reflux disease symptoms).

The use of IV PPI was not restricted to any particular specialty at any of the hospitals. Gastroenterologists and surgeons prescribed IV PPI the most often (36.3% and 19.4%, respectively), but internists, intensivists, surgeons and emergency physicians each prescribed over 10% of the total.

Administration of IV PPI

The majority of patients received an initial IV bolus of pantoprazole, either 80 mg (82.2%) or 40 mg (16.3%). Ten patients (1.2%) received no initial bolus but were started immediately on infusion therapy. In a number of these cases, an initial bolus was ordered but was either not given or not recorded as being administered.

TABLE 1
Patients receiving an intravenous proton pump inhibitor (IV PPI) for known or suspected upper gastrointestinal (UGI) bleeding: Demographics and prescribing practices

Patients receiving IV PPI (n)	854
Mean age (years ± SD)	63.2±17.6
Female, n (%)	326 (38)
Median length of stay (days, range)	10 (1–368)
Comorbidity ≥2 organ systems, n (%)	456 (53)
Admission for gastrointestinal bleed or bleed within 48 h of admission, n (%)	501 (58.7)
Risk factors for bleeding peptic ulcer disease (PUD), n (%)	
History of PUD	185 (21.7)
Use of nonsteroidal anti-inflammatory drugs	216 (25.3)
Concurrent multisystem organ failure	67 (7.8)
Intensive care unit admission	109 (12.8)
Prescribing physician, n (%)	
Gastroenterologist	309 (36.3)
Surgical specialty	166 (19.4)
General internist	140 (16.4)
Intensivist	120 (14.1)
Emergency physician	118 (13.8)
Indication for IV PPI, n (%)	
Suspected UGI bleeding	778 (91.1)
Other (gastroesophageal reflux disease, stress ulcer prophylaxis)	76 (8.9)
Administration of IV PPI, n (%)	
Initial bolus 80 mg pantoprazole	702 (82.2)
Initial bolus 40 mg pantoprazole	139 (16.3)
Other initial bolus	3 (0.3)
No initial bolus	10 (1.2)
Continuous infusion	721 (84.4)
No continuous infusion (intermittent boluses)	133 (15.6
Mean duration of IV PPI infusion (hours ± SD)	84.0±130.2

Eighty-four per cent of the patients received a continuous infusion of IV PPI (8 mg/h in 99%) following their initial bolus (Table 1). The remainder received intermittent boluses once, twice or three times daily.

Endoscopy

Five hundred eighty-eight patients (69%) underwent upper endoscopy. Evidence of PUD was found in 58% of these patients (Table 2). Of those patients with PUD, 147 (43%) had high-risk ulcer stigmata, of which 93% received some form of endoscopic therapy (injection, coagulation or hemoclips). The remainder of the patients' endoscopic findings included erosions (20%), varices (7%) or other causes of bleeding (10%). Endoscopy was normal in 6% of the patients.

Timing of IV PPI administration with respect to endoscopy

The majority of patients who had endoscopy (57%) had their IV PPI administered in advance of the procedure (Table 3). These patients had a mean of 18.6 h of IV PPI infusion administered before endoscopy.

At endoscopy, 46 (13.8%) of the 334 patients who had IV PPI given in advance were found to have high-risk bleeding PUD stigmata. The IV PPI infusions were continued in these patients after endoscopic therapy, in accordance with current evidence.

TABLE 2
Endoscopic findings

All endoscopies (n=588)	n	%
Peptic ulcer disease	342	58.2
Arterial bleeding (1a)	17	2.9
Oozing (1b)	68	11.6
Nonbleeding visible vessel (2a)	62	10.5
Total high-risk lesions	147	25.0
Endoscopic therapy on high-risk lesions	136/147	92.5
Erosions	118	20.1
Varices	39	6.6
Vascular lesions	12	2.0
Mallory-Weiss tear	19	3.2
Other	25	4.3
Normal	33	5.6

TABLE 3
Timing of administration of intravenous proton pump inhibitors (IV PPI) in endoscoped patients

IV PPI timing with respect to endoscopy	
All endoscoped patients (n)	588
IV PPI started before endoscopy, n (%)	334 (57)
Mean duration of IV PPI infusion before endoscopy (h ± SD)	18.6±16.5
IV PPI started after endoscopy, n (%)	254 (43)

The remaining 288 patients (86.2%) with advance IV PPI had low-risk PUD lesions or non-PUD lesions. Although IV PPI infusion has not been investigated in this population, the infusions were continued after endoscopy in 164 of these patients (56.9%), for a median of 49.9 h (range 1 h to 1003 h).

Outcomes

Mean transfusion requirements for all 854 patients were 4.8 units. For those with subsequently diagnosed PUD the transfusional requirements were even higher (5.5±7.1 units). Among all patients who received IV PPI during the study period, 30-day all-cause mortality was 16.3%. The mortality rate was lower among patients with PUD (11.1%). The rebleeding and surgery rates for patients with PUD were 24.9% and 2.3%, respectively. Over 50% of the rebleeding occurred in the first 24 h after endoscopy (Table 4).

DISCUSSION

UGI bleeding accounts for over 150 hospitalization admissions per 100,000 persons in the general population, with a case-fatality of 5%. Of these, approximately one-half are secondary to PUD (14,15). In those which have high-risk ulcer stigmata, endoscopic treatment has been shown to reduce recurrent bleeding, need for surgery and death (16,17). The advent of PPIs has greatly improved the treatment of PUD, but their adjunctive role in the setting of acute hemorrhagic peptic ulcer is only recently coming into focus.

Gastric acid plays a central role in the pathogenesis of PUD. Adequate clot formation requires platelet aggregation and plasma coagulation. Both of these steps are inhibited in vitro in the presence of acid and pepsin when the pH drops below 6.8. Platelet disaggregation and clot lysis occur when the pH is below 5 (8-10,18). Therefore, maintenance of clot

TABLE 4
Outcomes of patients receiving an intravenous proton pump inhibitor

Outcomes	
Patients with peptic ulcer disease only (n)	342
Rebleed, n (%)	85 (24.9)
Within 24 h of initial stabilization, n (%)	48 (14)
Surgery, n (%)	8 (2.3)
Intensive care unit admission, n (%)	22 (6.4)
Death, n (%)	38 (11.1)
All endoscoped patients (n)	588
Rebleed, n (%)	120 (20.4)
Within 24 h of initial stabilization, n (%)	64 (10.9)
Surgery, n (%)	8 (1.4)
Intensive care unit admission, n (%)	48 (8.2)
Death, n (%)	66 (11.2)
Overall (n)	854
Surgery, n (%)	23 (2.7)
Intensive care unit admission, n (%)	82 (9.6)
Death, n (%)	139 (16.3)

integrity and hemostasis relies on maintenance of near-neutral intragastric pH (8).

Antisecretory therapy in the management of acute bleeding peptic ulcers has previously focused on histamine H_2 receptor antagonists (H_2RAs), but the results have been disappointing. Both a meta-analysis (19) and large randomized controlled trial (20) failed to show any reduction in recurrent bleeding rates. These findings may be due to the rapid onset of tolerance to the H_2RAs (21,22), and their subsequent inability to maintain high intragastric pH, even with continuous infusion (11).

PPIs are much more potent inhibitors of acid secretion (23). However, oral dosing of PPI using standard doses may take several days to achieve adequate acid suppression; this greatly reduces their usefulness in the setting of acute hemorrhage. This limitation may be overcome in part by giving higher doses: a controlled trial of high-dose oral PPI given twice daily was associated with a decreased risk of recurrent bleeding in patients who had high-risk ulcers (visible vessel or adherent clots) (5). These patients did not undergo endoscopic therapy; however, the applicability of these results to patients who do receive such therapy is unclear.

IV preparations of PPI have only recently been approved for use in the United States. Experience from other countries has been positive: a large study by Lau et al (6) in 2000 included 240 patients randomized to IV omeprazole or placebo following endoscopic therapy. Recurrent bleeding was significantly lower in patients receiving omeprazole (6.7% versus 22.5%), a finding that led to early termination of the trial.

In clinical practice outside of trials, endoscopy may not be available on demand. Patients presenting at night or on weekends with acute UGI bleeding may typically wait up to 24 h or longer for endoscopy. This has been confirmed by the Canadian RUGBE trial, in which the mean endoscopy time from presentation in nonvariceal UGI bleeding in 1869 patients was 24 h (13).

Recently, we have developed a statistical model using a hypothetical cohort of 1000 patients comparing a strategy of empirically treating all patients presenting to the emergency department with IV PPI infusion and endoscopic treatment versus endoscopic treatment alone (12). Based on the expected frequencies of endoscopically treatable ulcers and the efficacy of IV PPI from the study by Lau et al (6), significant cost savings can be realized with the use of IV PPI. This model was based on the assumption that all patients received endoscopic examination within 24 h and that only PUD with high-risk stigmata gained benefit from IV PPI. Interestingly, logistic regression from RUGBE has now suggested that the benefit of high-dose acid suppression may extend beyond high risk PUD to include all patients with nonvariceal UGI bleeding. This expansion of benefit in IV PPI would give further support to previous cost analysis because the benefit would be expanded over the assumptions in the models.

Our initiative in Vancouver was started to examine the clinical uses and prescribing practices of IV PPI in six urban tertiary care hospitals. All patients with suspected UGI bleeding who received IV PPI from November 1999 (the date IV pantoprazole was placed on formulary in British Columbia) to June 2001 were reviewed. Endoscopic findings were recorded and correlated with administration of IV PPI and continuation or discontinuation of the IV pantoprazole postprocedure.

In an unrestricted setting, we have demonstrated that IV PPI is commonly used, and its use has been primarily for suspected UGI bleeding. Furthermore, it has usually been administered appropriately, with a bolus and continuous infusion in most patients at both academic and community-based sites. Over 55% of patients received their IV PPI before endoscopy. Although significant benefit has not been demonstrated in the use of IV PPI before endoscopy (versus postendoscopy), our cost analysis has suggested that it may be cost-effective. Additionally, because RUGBE has demonstrated that most nonvariceal UGI bleeding sources may benefit, more liberal use of IV PPI before endoscopy may be justified. Further data to substantiate this finding are required. Additionally, because patients with low-risk lesions have low rebleeding and mortality rates, even if IV PPI does decrease rebleeding it may have limited clinical implications.

As demonstrated in previous studies of UGI bleeding, over 50% of our patients had PUD (13,24). The mortality rates, however, appear to be higher than other databases. This may be secondary to the patient groups evaluated. Because we were only evaluating the use of IV PPI, it appears the patient group was an 'ill' one. This is supported by the high comorbid disease and number of transfusions required per patient. It would appear that IV PPI was being used in patients who were critically ill with significant blood loss. It would be logical to suggest that, when a new pharmaceutical agent becomes available, it would be more likely to be used in the more critically ill patient in an effort to use all available therapies to improve outcomes. The same explanation would likely apply to the high incidence of rebleeding seen in this study.

With regard to resource utilization, it would appear that the biggest area of concern in the present study is the fact that 56% of patients who had low-risk ulcer stigmata had their IV PPI continued despite a lack of evidence for IV PPI use in this patient population. It was continued for a mean of approximately 50 h. Education in this area would likely lead to earlier discontinuation of the medication, resulting in significant cost savings.

Further research on the effects and timing of IV PPI on the outcome of patients with bleeding peptic ulcers is needed, particularly in the North American context. Additionally, the role of oral PPI in the setting of acute hemorrhage needs to be better defined. Future studies should guide our management of these patients, but presently acid suppression is being widely used for UGI bleeding, in many patients, before endoscopic assessment.

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