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Oral rabeprazole vs. intravenous pantoprazole: a comparison of the effect on intragastric pH in healthy subjects

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SUMMARY

Background
Intravenous pantoprazole is often administered inappropriately to hospitalized patients who can take oral medications.

Aim
To compare the antisecretory effects of oral rabeprazole and intravenous pantoprazole in healthy subjects.

Methods
In a double-blind, double-dummy, two-way crossover study, 38 *Helicobacter pylori*-negative volunteers were randomized to oral rabeprazole 20 mg or intravenous pantoprazole 40 mg daily for 3 days followed, after a 14-day washout period by the comparator treatment. Intragastric pH was recorded continuously for 24 h at baseline and on days 1 and 3 of each treatment period.

Results
The mean (95% CI) percentage of the 24-h recording with gastric pH >4 was higher with rabeprazole than with pantoprazole on day 1: 37.7% (30.6–44.8%) vs. 23.9% (20.0–27.8). The mean percentage times with pH >3 and >4 for all intervals assessed were greater and the median 24-h intragastric pH values were higher with rabeprazole than with pantoprazole on days 1 and 3. The mean acidity index was lower with rabeprazole on days 1 and 3.

Conclusions
Oral rabeprazole 20 mg produced greater acid suppression than intravenous pantoprazole 40 mg. Therefore, it may be an appropriate and effective alternative in patients who can take oral medication.

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INTRODUCTION

Oral proton pump inhibitors (PPIs) achieve high levels of acid suppression and high healing rates in erosive oesophagitis and peptic ulcer disease although there is some dose-related variability observed between PPIs.[1–4] Currently, intravenous (IV) PPIs may be administered to patients who cannot take oral medications or to those who require rapid, prolonged acid suppression for the acute management of non-variceal upper gastrointestinal (GI) bleeding and prevention of re-bleeding after endoscopic haemostasis.[5–10] At present, pantoprazole is the only IV PPI available in Canada. The clear advantages of an IV PPI, such as the rapid onset of action, are of less benefit for the healing of erosive oesophagitis than for the prevention of recurrent upper GI haemorrhage. There has been an increase in the inappropriate use of IV PPIs due, in part, perhaps, to clinicians' concerns that oral therapy may be less effective than IV therapy.[11] In general, continuous IV infusion of a PPI produces greater acid suppression than intermittent oral administration. However, intermittent IV administration of a PPI is not necessarily more effective than an oral PPI and, in addition, parenterally administered agents may be associated with risks, such as infection, pain or fluid overload, as well as with increased costs of preparation and administration. Thus, it would, in principle, be preferable to administer PPIs orally for indications other than prevention of recurrent upper GI haemorrhage; however, this requires clear documentation that the oral PPI is at least as effective in suppressing gastric acid as the comparator IV PPI. Furthermore, the comparison should be based on an assessment of parameters that are relevant to the healing of erosive oesophagitis, the most common indication for PPI therapy; in this context, the proportion of the 24-h recording period during which intragastric pH is >4 is a surrogate marker for the healing efficacy of acid suppressive medications.[12, 13]

One limitation of an intragastric pH threshold parameter, such as time with a gastric pH >4, is that it does not quantify the increase in potential for harm as gastric pH falls to various levels below 4.[14, 15] The acidity index (AI), reflects acid exposure, calculated as a function of hydrogen activity $[H^+]$ in the stomach, and it is intended to provide greater weighting to those periods during which pH is lower and the $[H^+]$ is logarithmically greater. It is easy to calculate, and is thought to provide an accurate assessment of intragastric acidity. In addition, AI has been demonstrated to have a strong correlation ($r = 0.93$) with integrated intragastric acidity [area under the curve (*AUC*) of the pH–time curve] and a logarithmic relationship ($r = 0.78$) with percentage of time pH < 4.[14] It has, therefore, been proposed that AI should be reported in conjunction with the percentage of time pH > 4 and median pH, to give a more complete description of the degree of acid suppression.

Clinical pharmacodynamic evaluations of IV and oral pantoprazole have concluded that they are equipotent at increasing 24-h intragastric pH, with the percentage of time pH > 4 on the fifth day of dosing reported as 42% and 38%, respectively, with a mean difference between the treatment routes of only 4.4% (90% CI: 0.6–8.3).[10, 16, 17] The equipotency of oral and IV pantoprazole formulations has also been confirmed in a study of gastro-oesophageal reflux disease (GERD) patients.[18] Additionally, it has been demonstrated that oral rabeprazole produces greater acid suppression than oral pantoprazole, measured as the percentage of the 24-h period during which intragastric pH > 4.[19, 20]

In Canadian clinical practice, for patients with erosive oesophagitis, the conversion from IV to oral therapy generally occurs within 3 days; therefore, a 3-day treatment period is an appropriate time frame during which to document the equivalence of oral and IV PPIs.

The present study tests the hypothesis that oral rabeprazole (20 mg daily) produces acid suppression equivalent to that produced by IV pantoprazole (40 mg daily), determined by calculating the proportion of 24-h recording period during which intragastric pH is >4 on the first day of drug administration. The two treatments are to be considered equivalent if the difference in the proportions of time during which intragastric pH is >4 on the first day is less than 10%.

MATERIALS AND METHODS

Subjects

This single-centre Canadian study was conducted at Hamilton Health Sciences (McMaster University Medical Centre), Hamilton, Ontario. The study was conducted in accordance with the Declaration of Helsinki (1975) and ICH[21] guidelines after the protocol had been approved by the institutional Ethics Committee. All subjects gave written informed consent. All subjects were healthy adult volunteers who were *Helicobacter*

pylori-negative as determined by ^{13}C-urea breath test (UBT). Breath samples were analysed at the GI Breath Testing Laboratory, Hamilton Health Sciences, by isotope ratio mass spectrometry, according to standard protocols. Subjects had no clinically significant disease as determined by medical history, physical examination and laboratory safety tests. All females of childbearing potential had a negative serum β-hCG test, and none was lactating. Subjects were required to have a body mass index (BMI) between 18 and 33 kg/m^2 and a weight between 50 and 135 kg; they were either non-smokers or they smoked <10 cigarettes/day and were able to adhere to smoking restrictions during the study. Exclusion criteria included significant concurrent disease or clinical illness within 14 days of the initial screening visit and use of prescription medicines within 14 days of the start of the study (except oral contraceptives, topical medications for skin conditions and nasal sprays for allergy relief). No H_2-receptor antagonists, PPIs, prokinetics, antibiotics, or bismuth were allowed within 28 days of the screening ^{13}C-UBT.[22] Over-the-counter medications were not allowed within 7 days of the start of the study, with the exception of acetaminophen (up to a daily maximum of 2 g for acute, self-limited conditions, e.g. headache, and non-prescription optic/nasal allergy medications or topical medications for skin conditions). Subjects were excluded if they had participated in another investigational drug or device study within 30 days of the initial screening visit.

Study design

This was a randomized, double-blind, double-dummy, two-way crossover study. Subjects were screened to determine eligibility and had baseline oesophageal manometry to localize the lower oesophageal sphincter (LES) relative to the nares; this allowed placement of the pH probe 10 cm below the LES for the baseline and subsequent pH recordings. Baseline 24-h intragastric pH monitoring was performed within 14 days prior to the first treatment period to confirm normal acid secretory patterns, and for exploratory AI analyses. Subjects were randomly assigned, in equal numbers, to one of two sequence groups; the sequence of treatments was such that each subject had received both regimens upon completion of the study. Each treatment period consisted of an oral tablet and an IV infusion administered once daily for 3 consecutive days, with a 14-day ($\pm$3) washout period between the two treatment periods. A 24-h intragastric pH recording was performed on the first and third days of each treatment period.

Study medication

Each subject first received either an oral tablet of rabeprazole 20 mg (Eisai Ltd, Teaneck, NJ, USA) and 100 mL of 0.9% sodium chloride for IV injection as placebo solution for pantoprazole, or IV pantoprazole 40 mg (Altana Pharma AG, Constanz, Germany) and a placebo oral tablet for rabeprazole, once daily for 3 days during each treatment period. An independent service generated the randomization schema. The treatment assignment, preparation of the IV solution and dispensing of all study medications were carried out by an independent nurse who was not involved in other study procedures. Pantoprazole solution for infusion, prepared and administered according to the manufacturer's directions, was reconstituted on the day of administration and used within 6 h of the initial puncture of the stopper. The IV solution was prepared by injecting 10 mL of 0.9% sodium chloride injection USP into the vial containing the lyophilized powder. This solution was then further diluted with 90 mL of 0.9% sodium chloride injection USP. The reconstituted solution was infused over a period of 15 min.[9] Placebo IV solution was prepared by puncturing the stopper of the infusion bag and labelling the bag in an identical manner to the active pantoprazole solution, with the same date and 6-h expiry time to maintain the blind, and this was infused over a 15-min period. Drugs were stored and prepared in an area with access restricted to the nurse involved in drug preparation. To maintain the blind, medication records were not collected until after the last patient had completed the final visit.

24-h intragastric pH monitoring

Subjects were fully ambulatory during the study and presented to the clinical investigational unit only for administration of study medication, and for insertion and removal of the electrode on pH monitoring days. Dietary and lifestyle restrictions during the study included fasting (neither food nor drink) overnight before dosing on the first and third day of each treatment period, until 1 h after dosing. Alcohol, caffeinated drinks, citrus fruits or their juices (including tomatoes and tomato juice), carbonated drinks (other

than lightly carbonated mineral water), smoking and vigorous exercise were prohibited from 48 h prior to the start of baseline 24-h intragastric pH recording period, as well as during each study medication treatment period from the first day of treatment until the morning after the last dose. No prescription medications or over-the-counter medications were permitted for the duration of the study, with the exception of those medications, listed above, that had been permitted during the period before the study. During the pH monitoring periods, subjects received a standard breakfast 1 h postdosing; other meals for that day were consumed outside the clinical research unit at standardized times (08:15, 13:00, 18:00 and 22:00 hours recommended). Each subject used a daily diary to record actual timing and description of meals.

Intragastric pH was recorded continuously for 24 h at baseline and on the first and third days of each of the two treatment periods (beginning immediately before dosing of medication), using a glass pH electrode (Ingold M440, Medtronic, Mississauga, ON, Canada) which was calibrated prior to each recording period using room temperature buffers of pH 1.07 and 7.01, as recommended by the manufacturer. The pH electrode was placed 10 cm below the LES, as described above. Intragastric pH values were sampled every 4 s, recorded with a Digitrapper pH 400 data recorder (Medtronic) and then downloaded to a proprietary format Medtronic pH data file before conversion to an ASCII file for analysis. Further analysis of pH data was performed according to established techniques using dedicated software for summary and graphical presentation. Intragastric pH values <0.8 or >10 were regarded as measurement artefacts (implausible data) and discarded from analyses; similarly, recordings were discarded if there were obvious abnormalities on visual inspection of the gastric pH curves by an investigator blinded to the treatment schedule.

Safety evaluation

A physical examination, including weight and vital signs, in addition to biochemistry and haematology blood tests were performed at baseline and study termination. Subjects were closely monitored for, and queried about adverse events throughout the study. All adverse events were assessed for severity and possible relationship to study drugs.

Statistics

The number of subjects was calculated to demonstrate, with 80% power, that the difference between IV pantoprazole and oral rabeprazole was ≤10% with respect to the percentage of time intragastric pH was >4 on day 1. Therefore, the hypothesis testing was defined as (H_o: $A_p - A_r \geq 10\%$ vs. H_1: $A_p - A_r < 10\%$). It was determined that 33 subjects were required, assuming that the standard deviation of the difference was 20% and that the one-sided test was carried out at the 2.5% significance level. A total of 38 subjects was enrolled to account for drop outs, including technical failures.

The rolling median of the 4-sec intragastric pH values over 15-min intervals was calculated and used as a smoothing procedure to generate 24-h pH profile plots at baseline (non-drug period), days 1 and 3. The calculated response statistics, after removal of implausible data included: the percentage of time when intragastric pH was >3, >4, >5, >6 and the median intragastric pH. These response statistics were calculated for baseline and for each treatment group on days 1 and 3 with the following predefined time intervals: 0–24, 0–14 and 14–24 h. Additionally, the proportion of subjects who maintained pH >3, >4, >5, >6 for at least 12 h and for at least 16 h of the 24-h period were calculated for days 1 and 3.

The primary analysis was carried out on the evaluable population, which included all randomized subjects who received at least one dose of drug in each treatment period, had a valid baseline 24-h pH recording, and a minimum of two-paired valid 24-h pH recordings (first day of dosing for each treatment period). Subjects with major protocol violations were excluded. A valid pH recording was defined as a minimum of 23 h, with <5% implausible values (<0.8 and >10). The primary end point (percentage of time pH > 4 on day 1 of dosing) was analysed using a mixed-model ANOVA with period, sequence and treatment as fixed effects and subject nested within sequence as random effect. No adjustment for carry over effect or baseline values was included in the analysis. Confidence intervals and *P*-values were used to assess the treatment differences. Secondary end points were analysed using a similar model to that used for the primary end point. Proportions of subjects with intragastric pH >3, >4, >5, >6 for more than 12 h, and for more than 16 h of the 24-h period on days 1 and 3 were analysed using a mixed logistic model with period, sequence and treatment as explanatory variables.

The formula used to calculate AI[14] for each 24-h measurement period was:

$$\mathrm{AI} = \sum [(\%T\mathrm{pH} < 4 - \%T\mathrm{pH} < 3) \times 1] [(\%T\mathrm{pH} < 3 - \%T\mathrm{pH} < 2) \times 10] [(\%T\mathrm{pH} < 2 - \%T\mathrm{pH} < 1) \times 100] [(\%T\mathrm{pH} < 1 - \%T\mathrm{pH} < 0.8) \times 1000]$$

A lower AI indicates higher intragastric pH for the time interval evaluated. The mean AI (95% CI) was calculated for oral rabeprazole and IV pantoprazole on the first and third days of dosing, with 95% CIs calculated for any differences between treatments, based on a similar model to that used for the primary response.

RESULTS

Subjects

In all, 38 subjects (63% male, 95% Caucasian) were randomized. Mean (±s.d.) age was 29 years (±9.9), weight 75.6 kg (±13.7), height 172 cm (±7.9) and BMI 25.4 kg/m^2 (±3.7). One patient withdrew consent after randomization but did not receive any doses of study medication. Of the remaining 37 subjects who completed the study, three subjects had an invalid 24-h pH recording on day 1 of the treatment period and an additional subject took an exclusionary non-steroidal anti-inflammatory drug on day 1 of the second treatment period, leaving 33 subjects evaluable for the primary efficacy analysis.

Intragastric pH

Plots of median intragastric pH over 24 h on days 1 and 3 are illustrated in Figure 1, with meal times indicated. The mean (95% CI) percentage of time with pH > 4 over the 24-h period was higher with oral rabeprazole than with IV pantoprazole on day 1: 37.7 (30.6–44.8%) vs. 23.9 (20.0–27.8) respectively. The mean difference (95% CI) was 13.9% (6.05–21.8). On day 1, the mean percentage time above pH thresholds of 3, 5, and 6 over the 24-h period was significantly higher for oral rabeprazole than for IV pantoprazole; this was the case as well during the overnight period (14–24 h) for pH thresholds of >3 and >4 (Figure 2). Overall, this difference in acid suppression between the two treatments was also reflected in the percentage time pH >3, >4, >5 and >6 for the time intervals studied on day 3 (Table 1). Rabeprazole maintained intragastric pH above 3 for at least 12 h on day 1 in 54.5% of subjects compared with 12.1% of pantoprazole subjects ($P = 0.0012$). On day 3, intragastric pH was maintained above 3 for at least 12 h in 91% of rabeprazole subjects compared with 55% of pantoprazole subjects ($P = 0.0043$). The same was true for pH above 4 on day 3. Also, rabeprazole had a significantly higher percentage of subjects with pH > 3 for at least 16 h of the 24-h period on day 3 (Table 2). On both day 1 and day 3, a significantly higher median intragastric pH was observed with oral rabeprazole compared with IV pantoprazole for all time periods (Figure 3). Figure 4 illustrates individual 24-h median pH curves by treatment for all evaluable patients on days 1 and 3. The effect of study period or treatment sequence was not statistically significant in any of the analyses, indicating that there was no carryover effect between periods (data not shown).

There was a significantly lower mean AI (95% CI) with rabeprazole compared with pantoprazole (Table 3) on days 1 [3625 (2963–4287) vs. 5597 (4865–6329)] and 3 [2154 (1723–2585) vs. 3657 (3092–4222)]. Individual 24-h mean AI values correlated strongly with the corresponding values for time with gastric pH > 4 (Figure 5) but, despite this, there was marked variation in AI values with respect to the acid exposure times.

Drug safety

No clinically important changes were observed in biochemistry, haematology or vital signs during the course of the study. There were no serious adverse events and 62% of subjects did not experience any adverse events. Adverse events were rated as moderate or greater in intensity in 22% of subjects (eight of 37) and were deemed to be related to study medication or study procedures. No adverse events resulted in study discontinuation.

There was no significant difference in the incidence of adverse events between the two treatments. The most commonly reported adverse events, regardless of relationship to study medication, were headache and vomiting for both rabeprazole and pantoprazole: it is not clear whether these were related to medication or to the pH-probe placement. Both drugs were well tolerated.

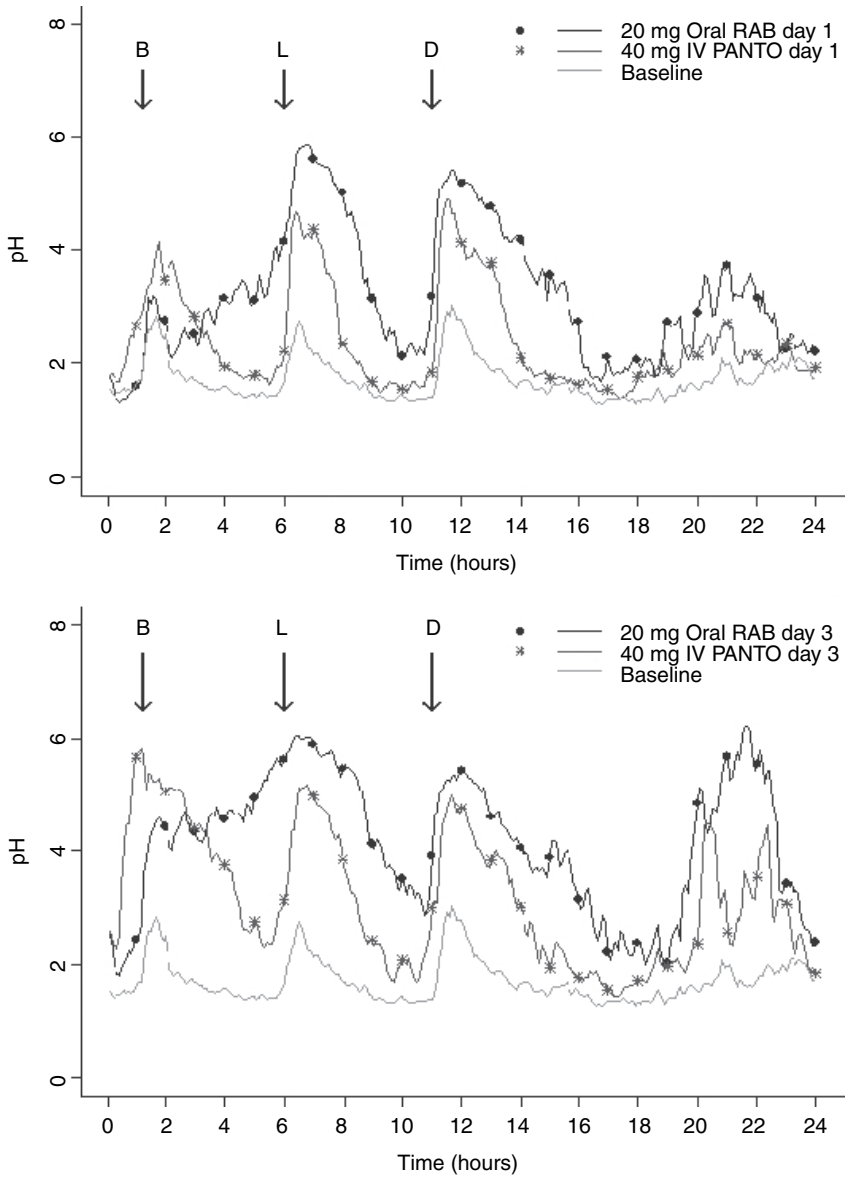

Figure 1. Median 24-h intragastric pH curves on days 1 and 3 by treatment regimen ($n = 33$). RAB, rabeprazole; PANTO, pantoprazole (B, breakfast; L, lunch; D, dinner).

DISCUSSION

Oral rabeprazole is more effective than IV pantoprazole on days 1 and 3; on both days, once daily administration of standard-dose oral rabeprazole achieved and maintained a higher intragastric pH than did a standard dose of IV pantoprazole. With respect to parameters predictive of success in the treatment of GERD[12, 13] (proportion of time with gastric pH >4.0), oral rabeprazole was more effective than IV pantoprazole and, for all other parameters (proportion of time pH greater than various pH thresholds, proportion of patients above pH thresholds for various time periods and median intragastric pH) there was also greater acid suppression with once-daily oral rabeprazole than with once daily IV pantoprazole. This was true during both 24-h periods, including the 10-h nocturnal periods.

The primary aim of the study was to show that oral rabeprazole is at least as effective as IV pantoprazole when administered once daily, as is usual for patients with erosive oesophagitis. The results show that, in fact, oral rabeprazole produces more prolonged acid suppression than IV pantoprazole in a population of healthy subjects such that rabeprazole maintains gastric pH above 4.0 for 3.3 h longer than pantoprazole.

These results are consistent with other gastric pH studies that have compared various oral

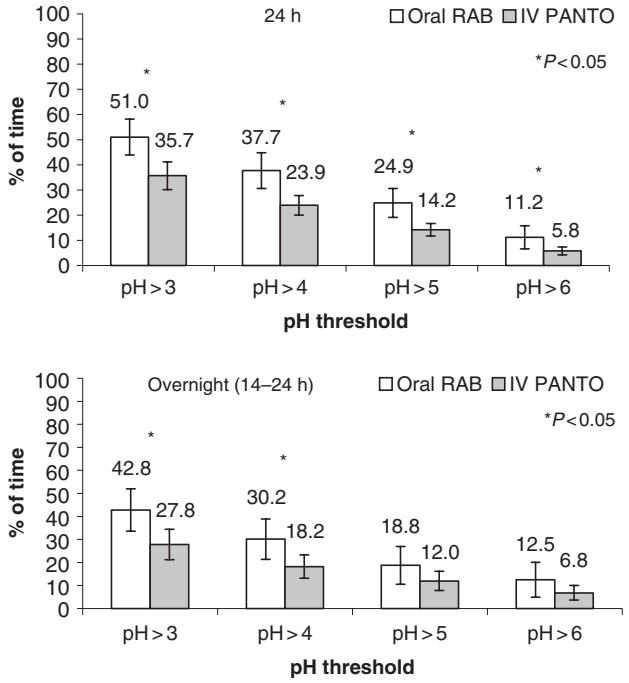

Figure 2. Day 1: (Top graph) complete 24-h recording (0–24 h) and (bottom graph) overnight recording (14–24 h). Mean percentage time during which intragastric pH >3, >4, >5 and >6 by treatment regimen (n = 33). RAB, rabeprazole; PANTO, pantoprazole. Note: 95% confidence intervals are represented by vertical lines.

PPIs[19, 20, 23, 24] with each other and compared IV with other oral PPIs.[1, 17] In a study of healthy *H. pylori*-negative volunteers, a single dose of oral rabeprazole 20 mg maintained pH > 4 for a greater proportion of the 24-h period than did oral pantoprazole 40 mg, lansoprazole 30 mg or omeprazole 20 mg.[19] In another study evaluating the pharmacodynamic effects of repeated doses of five PPIs in GERD patients, oral rabeprazole produced greater acid suppression (assessed by percentage of time pH > 4.0) than oral pantoprazole although no statistical comparison was presented in this analysis.[20] Other PPIs (lansoprazole and esomeprazole) have also demonstrated an ability to sustain intragastric pH above 4.0 on day 1 of dosing for significantly longer periods than IV pantoprazole.[1, 25]

The percentage time gastric pH is >4 with IV pantoprazole is lower in the present study than in earlier studies[17] measured on day 5 (42% vs. current finding of 23.9%) but is consistent with a previous study[25] that compared IV pantoprazole with oral esomeprazole. There may be a number of reasons contributing to discrepancies between studies including different study populations (healthy subjects vs. patients),[24] the use of antimony[1] rather than glass[16, 25] pH monitoring electrodes and the presence of *H. pylori*-positive subjects.[1, 17] The presence of *H. pylori* infection has been reported to increase the effect of PPIs in reducing gastric acidity,[26] a finding that is consistent across all PPIs regardless of route of administration.[27–29] The major reason for the baseline recordings in this study was to confirm that all subjects had a normal gastric acid secretory state; as in previous studies, the effect of the two PPI formulations was compared by comparing the recordings obtained during PPI administration. Adjustment of the pH values obtained during treatment using the baseline pH has not been necessary in the vast

Table 1. Mean percentage time (95% CI) during which intragastric pH >3, >4, >5 and >6 on day 3 of treatment (n = 33)

		Oral rabeprazole		IV pantoprazole	
pH Threshold	Time interval (h)	Mean percentage time	95% CI	Mean percentage time	95% CI
>3	0–24	68.4	63.5–73.4	51.5	46.3–56.7
	0–14	77.2	72.3–82.1	61.8	56.1–67.6
	14–24	56.2	47.8–64.6	37.0	30.3–43.8
>4	0–24	54.4	48.9–60.0	37.7	32.7–42.7
	0–14	62.30	56.3–68.3	45.0	39.6–52.2
	14–24	43.4	35.4–51.3	26.2	19.4–33.0
>5	0–24	38.1	32.2–44.4	24.8	20.5–29.1
	0–14	44.0	37.4–50.5	29.0	23.4–34.6
	14–24	29.8	22.5–37.1	18.8	12.3–25.3
>6	0–24	17.3	13.2–21.4	11.5	8.6–14.4
	0–14	15.4	11.9–19.0	10.6	7.8–13.5
	14–24	19.9	13.4–26.4	12.7	7.4–18.0

Table 2. Percentage of subjects (95% CI) with intragastric pH >3, >4, >5 and >6 for at least 12 h or16 h per day during treatment on days 1 and 3 ($n = 33$)

		Day 1				Day 3			
		Oral rabeprazole		IV pantoprazole		Oral rabeprazole		IV pantoprazole	
Time segment (h)	pH Threshold	%	95% CI	%	95% CI	%	95% CI	%	95% CI
≥12	>3	54.5	34.6–75.7	12.1	2.9–26.9	90.9	74.6–97.4	54.5	35.5–72.3
	>4	18.2	5.9–36.6	3.0	0.2–17.4	63.6	43.4–82.0	15.2	4.7–31.8
	>5	6.1	–	0	–	21.2	8.4–40.5	3.0	0.3–18.5
	>6	3.0	–	0	–	3.0	–	0	–
≥16	>3	9.1	–	6.1	–	39.4	22.1–59.2	3.0	0.3–19.2
	>4	6.1	–	0	–	6.1	0.7–22.1	3.0	0.2–18.2
	>5	3.0	–	0	–	3.0	–	0	–
	>6	0	–	0	–	0	–	0	–

95% confidence intervals calculated using a mixed logistic model to adjust for repeated measurements. Blank values for the CI indicate lack of information to estimate the model (zero observations in some of the required cross-classifications).

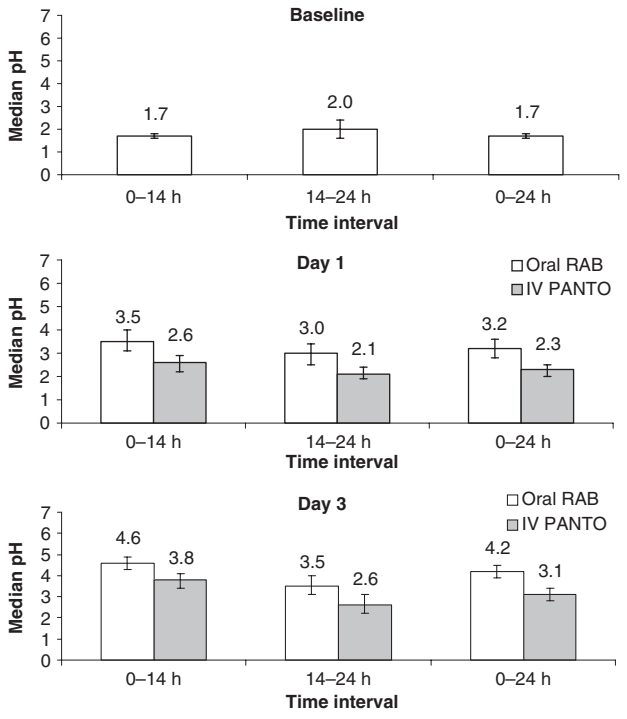

Figure 3. Median intragastric pH (0–24, 10–14 and 14–24 h) by treatment regimen for baseline (top panel) and days 1 (middle panel) and 3 (bottom panel). RAB, rabeprazole; PANTO, pantoprazole. Note: 95% confidence intervals are represented by vertical lines.

majority of previous studies and, in this study, use of the baseline pH would have had little, if any effect, as the reference values would have been identical, because they would have been derived, in all cases, from the same baseline gastric pH recordings.

The rationale for evaluating once daily PPI therapy is related to its relevance to the management of GERD in the general population. The use of *H. pylori*-negative subjects is reasonable as the current infection rate among Canadians suffering from acid reflux symptoms is 25–30%,[30] hence, 75% of GERD patients in Canada would be expected to be *H. pylori*-negative. Additionally, because the effect of a PPI is less in *H. pylori*-negative patients,[27] the *H. pylori*-negative population investigated in this study provided more stringent conditions under which to detect differences in acid suppressive activity between treatment groups. The study was conducted in healthy subjects, and the results should therefore be extrapolated with caution to patients in an intensive care unit (ICU) and those who are being treated for upper GI bleeding. All the subjects in this study had normal baseline pH data and thus normal gastric secretory function, unlike some ICU patients in whom gastric acid secretion may be compromised by severe concomitant illness. Although, there is no indication from previous studies that differences between PPIs are limited to a specific subset

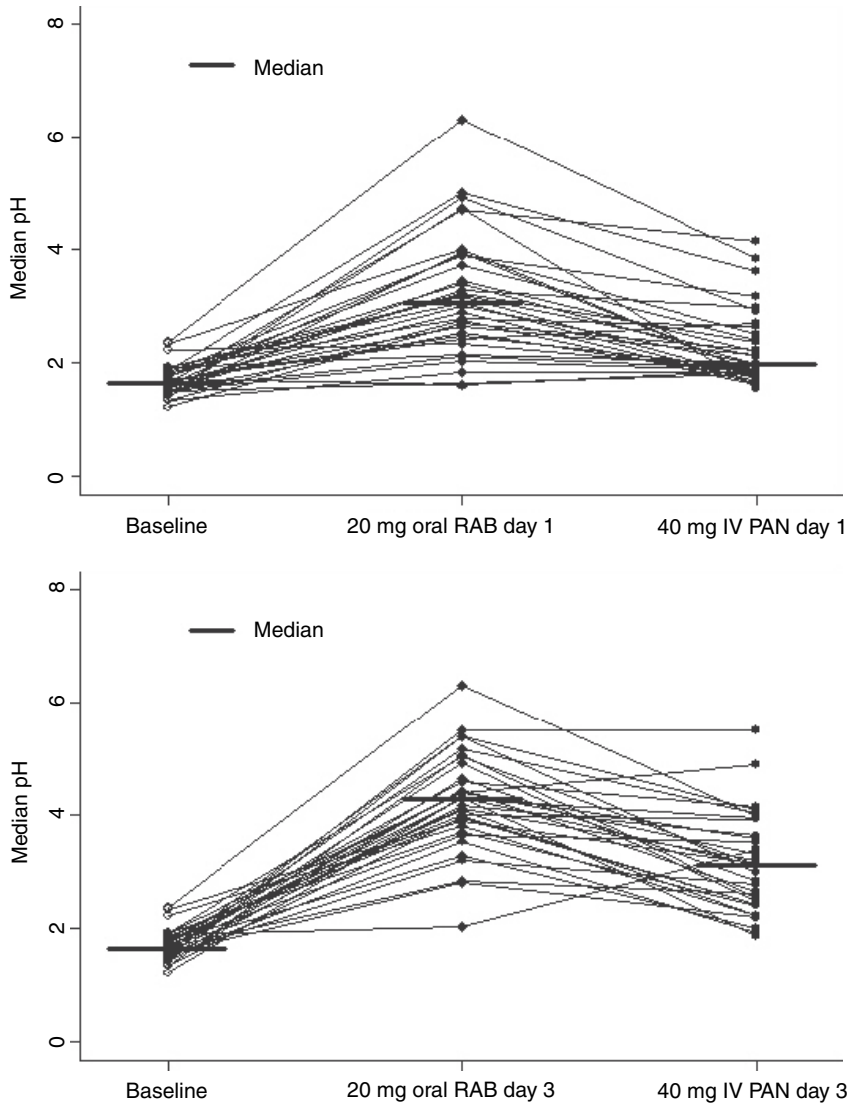

Figure 4. Individual 24-h intragastric pH by treatment regimen for all patients on days 1 (top) and 3 (bottom; $n = 33$).

Table 3. Comparison of mean change from baseline for acidity index (AI; 95% CI) by treatment regimen ($n = 33$)

	Oral rabeprazole		IV pantoprazole		
	Mean change from baseline	95% CI	Mean change from baseline	95% CI	*P*-value
Day 1	−4981	−6069 to −3892	−3009	−4134 to −1884	0.0117
Day 3	−6451	−7580 to −5323	−4948	−5943 to −3953	0.0432

of individuals, these results should be tested in ICU patients who are able to take PPIs orally or enterally, recognizing that multiple 24-h gastric pH recordings, such as those required by the present study protocol, may not be well tolerated by or acceptable to hospital in-patients.

As any advantage of an IV preparation should be evident only in the early part of the therapy, a 3-day time frame was chosen for the study. The results clearly indicate that oral rabeprazole produces acid suppression, that is at a minimum, equivalent to that produced by IV pantoprazole on day 1. In fact, oral

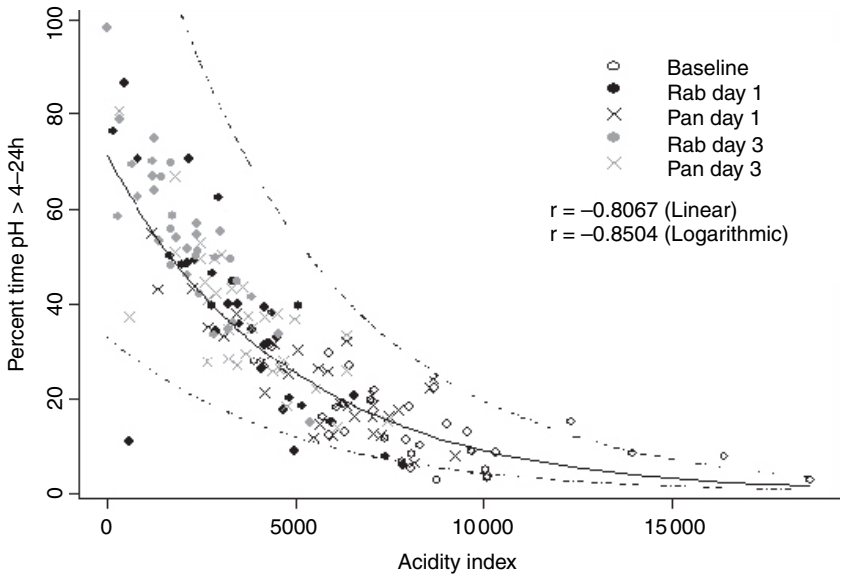

Figure 5. Time (percentage 24-h recording) with gastric pH > 4.0, compared with the corresponding acidity index (AI) for each individual recording (baseline and treatment), showing the best fit, logarithmic regression line (solid line) and the 95% confidence intervals for the best fit (dotted lines).

rabeprazole produced greater or more prolonged acid suppression than IV pantoprazole for all key parameters. As there was no difference between oral rabeprazole and IV pantoprazole by day 3 of treatment, it is very unlikely that there would be any significant longer-term differences between the oral and IV therapies. Furthermore, assessment of acid suppression over a longer period would have little clinical relevance, as IV PPI therapy is rarely administered for more than a few days in most patients. Overuse of IV PPIs is often related to continued use in patients who are able to tolerate oral medications and this has significant healthcare cost implications.[11, 31, 32] IV pantoprazole is indicated for conditions requiring rapid reduction of gastric acid secretion in hospitalized patients who cannot tolerate oral medication.[9] The present study shows that oral rabeprazole is, at a minimum, no less effective than IV pantoprazole, at least in healthy subjects, and it is, therefore, a reasonable alternative to IV PPI therapy for patients who can take oral medications.

The percentage time with pH > 4 is well correlated with healing for patients with erosive oesophagitis and it is an accepted measure of treatment effect.[13, 33] The AI – the pH-adjusted acid exposure time – provides an inverse measure of acid suppression effect and it has been postulated that it is a better index of the injurious potential of acidic gastric contents.[14] Although this was only an exploratory, descriptive analysis in the present study, the data did indicate that oral rabeprazole produced a greater reduction in the AI than did IV pantoprazole. Given the strong correlation with integrated intragastric acidity, AI merits further study as a marker of treatment effect in acid-related disorders; routine incorporation into future clinical studies will enable a more thorough evaluation of AI's predictive role.

Studies with IV PPIs as initial therapy followed by oral PPI therapy for erosive oesophagitis have shown comparable healing rates at 8 weeks to those reported with oral rabeprazole alone.[4, 34, 35] The results of the present study are consistent with those of previous studies which have reported that oral rabeprazole is effective in both acute and long-term management of acid-related disorders.

The demonstration, in this appropriately powered study, that oral rabeprazole produces greater acid suppression than IV pantoprazole during the early phase of drug administration (the first 3 days), provides a strong rationale for an early switch from IV pantoprazole to oral rabeprazole in the acute management of oesophagitis patients who are able to take oral medications with the expectation that longer-term therapy with oral rabeprazole would heal and prevent the recurrence of erosive GERD.[35–37] However, the implications of the present study's results for the management of GERD in patients requiring initial IV PPI therapy should be confirmed by further, clinical studies in patients with GERD. Evaluation of the role of switching from IV to oral PPIs in patients with upper GI haemorrhage will require additional, high-dose pharmacodynamic studies, followed by appropriate clinical studies in the relevant patient populations. Also, if other IV PPIs become available or widely used, it may be necessary to conduct more studies in healthy

subjects or in patients to determine relative efficacy and thus other treatment management options.

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