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Optimizing the Intragastric pH as a Supportive Therapy in Upper GI Bleeding

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Acid inhibitory therapy has long been considered of no benefit for upper GI bleeding. The reason was that achlorhydria in the stomach could not be achieved with any single or combination of acid inhibitory drugs. The introduction of proton pump inhibitors has, for the first time, allowed the physician to temporarily achieve achlorhydria by large doses of intravenously applied proton pump inhibitors. The first placebo-controlled clinical trials have shown that, indeed, an intragastric pH of near 7 can significantly improve the clinical outcome of upper GI bleeding. Pharmacokinetic studies with proton pump inhibitors have shown that a bolus of 80 mg pantoprazole or omeprazole followed by immediate continuous infusion of eight mg per hour will result in an intragastric pH of 7 within 20 minutes. This intragastric pH optimizes the different steps of hemostasis in the stomach.

INTRODUCTION

For decades, physicians have tried to influence intragastric bleeding by physical and pharmacological means. No significant influence by the many approaches could be achieved until recent endoscopic techniques brought a breakthrough by stopping the active bleeding by means of injection of vasoconstricting and sclerosing agents or by heat coagulation [1-6]. Through these techniques, emergency surgery has been significantly reduced. However, after initial endoscopic hemostasis, rebleeding still occurs in up to 20 percent of patients, and surgery is still necessary in some of these patients.

Optimization of the physiological conditions for hemostasis has been the aim of many pharmacological approaches. None of these approaches has resulted in convincing effects. Reduction of blood flow was one of these approaches for which vasopressin, somatostatin and secretin have been applied [7-11]. Pepsin inhibitors were introduced with the aim of preventing clot digestion [12]. Inhibition of thrombolysis was tried by the application of tranexamic acid [13]. This method was so successful that not only thrombolysis was inhibited, but thrombosis appeared in many parts of the body preventing further use of this approach. Increasing intragastric pH was the final pharmacological approach, which also yielded disappointing results. Antacids, anticholenergics and histamine receptor antagonists were without effects because they could not reliably achieve that elevation of the intragastric pH that is necessary to significantly influence the physiology of hemostasis [14, 15, 16]. The failure of the H_2-receptor antagonists is explained by the rapid onset of tolerance towards these drugs [17-19].

Green and coworkers have shown that platelet aggregation and blood coagulation are optimal at pH 7.4. Below pH 5.9, platelet aggregation, the initial step of hemostasis, is practically non-existent [20]. Freshly formed clots can easily be digested by gastric pepsin

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as long as there is any acid left in the stomach [21]. The physiology of hemostasis demands pH values near 7. Only proton pump inhibitors can reliably achieve such values if sufficient doses are given. In early studies with intravenous omeprazole for peptic bleeding, insufficient doses were used. But even these doses showed significant improvement over H_2-receptor antagonist therapy [22, 23]. Pharmacokinetic studies with omeprazole concluded that an initial bolus injection of 80 mg followed by a continuous infusion of eight mg per hour was optimal with regard to reduction of intragastric acidity [24, 25, 26]. This dosage regimen was investigated in two large placebo-controlled trials and revealed a significant advantage for the omeprazole therapy with respect to frequency of surgery, need for the endoscopic interventions, the severity and the duration of bleeding, as well as the need for blood transfusions [27, 28].

The aim of this study was to investigate the optimal mode of application and dosing of intravenously administered pantoprazole, a new proton pump inhibitor.

SUBJECTS AND METHODS

Medication

The pantoprazole i.v. formulation (Byk Gulden, Konstanz, Germany) was diluted using 0.9 percent NaCl solution and administered as a dilution of four mg/hr. Bolus injections of 40 mg (10 ml) or 80 mg (20 ml) were administered within two minutes; the long-term infusions were given at a rate of one ml/hr (four mg/hr) or two ml/hr (eight mg/hr). Doses stated in mg refer to pantoprazole as the free acid; the drug, however, was administered as the sodium salt.

Dietary

The subjects took their last meal at 6:00 p.m. the day prior to the investigation and remained fasting throughout the treatment period on the next day. Drinking of water was allowed.

pH metry

Intragastric pH was continuously recorded using Digitrappers MKII/MKIII (Synectics Medical, Stockholm, Sweden) and glass electrodes M440 (Ingold, Urdorf, Switzerland). The electrodes were calibrated before use at pH 1 and 7 using commercially available buffers. The probe was inserted into the nose and moved downward until the pH turned from neutral to acid (when passing the cardia). The probe was then pushed forward another six cm and fixed at the nose.

Laboratory

Laboratory values were determined directly before and one day after the investigation; these included routine hematologic studies, assay of serum enzymes indicative of liver function, serum electrolyte measurements, and serum creatinine determination.

SUBJECTS

Repeated bolus injections

Eight healthy volunteers (four males; four females) were admitted to the study. Six subjects completed the study protocol correctly. Their ages ranged from 26 to 42 years, and their body weights were between 50 and 80 kg. Each of them underwent a treatment period of 48 hours with eight hourly bolus injections of 40 mg each, preceded by a loading dose of 80 mg (bolus) in the beginning. Intragastric pH was continuously recorded over 48 hours.

Long-term infusion (four mg/hr)

Six healthy volunteers (three males; three females), with ages ranging from 24 to 30 years and body weights between 60 and 80 kg, underwent two treatment periods of 48 hours each in randomized order under double-blind conditions. In one period, a loading dose of 40 mg (bolus) was administered, subsequently followed by a long-term infusion of four mg/hr. In the other period, placebo (0.9 percent NaCl solution) was administered instead of pantoprazole. Intragastric pH was continuously recorded over 48 hours in both periods.

Long-term infusion (eight mg/hr)

Eight healthy volunteers (four males; four females), with ages ranging from 25 to 32 years and body weights between 50 and 76 kg, underwent two treatment periods of 24 hours each in randomized order. In both periods, separated by a wash-out interval of at least one week, a long-term infusion of eight mg/hr was administered. In one period, the loading dose of 80 mg was given as a bolus injection, in the other period it was given as a two-hour infusion (the latter means that the infusion rate was 48 mg/hr during the first two hours).

RESULTS

Intragastric Acidity

The median 24 hour profiles of intragastric pH for the four different modes of application are shown in Figures 1 to 3. All doses caused a significant reduction of intragastric acidity.

The percentage of time with an intragastric pH above 3, 4, 5 and 6 is shown in Table 1. Intermittent bolus injections do not significantly raise the pH above 3.0 (Figure 1). Continuous infusion with a significantly lower total 24-hour dose is more effective in increasing the intragastric pH, showing an improvement on the second day of infusion (Figure 2). Doubling the hourly infusion rate to eight mg per hour achieves the desired breakthrough (Figure 3). There is a marked difference between the effect of the two different loading doses. Spreading the loading dose of 80 mg over two hours results in a retarded pH increase, reaching the optimal pH only after 12 hours. Applying the initial loading dose as a bolus given within two minutes achieves the desired pH within 20 minutes (Figure 3). The optimal mode of application for reaching the intragastric pH necessary for

Table 1. Comparison of four different modes of pantoprazole application with respect to median percent time above pH 3.0, 4.0, 5.0 and 6.0.

Median percent time above	Placebo		40 mg bolus every 8 hours		Infusion 4 mg/hr 40 mg initial bolus		Infusion 8 mg/hr 48 mg/hr initial 2 hours	Infusion 8 mg/hr 80 mg initial bolus
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2		
pH 3.0	22	6	49	78	88	100	94	99
pH 4.0	7	0	20	47	54	85	82	99
pH 5.0	1	0	5	16	24	42	55	94
pH 6.0	1	0	0	1	13	10	31	84

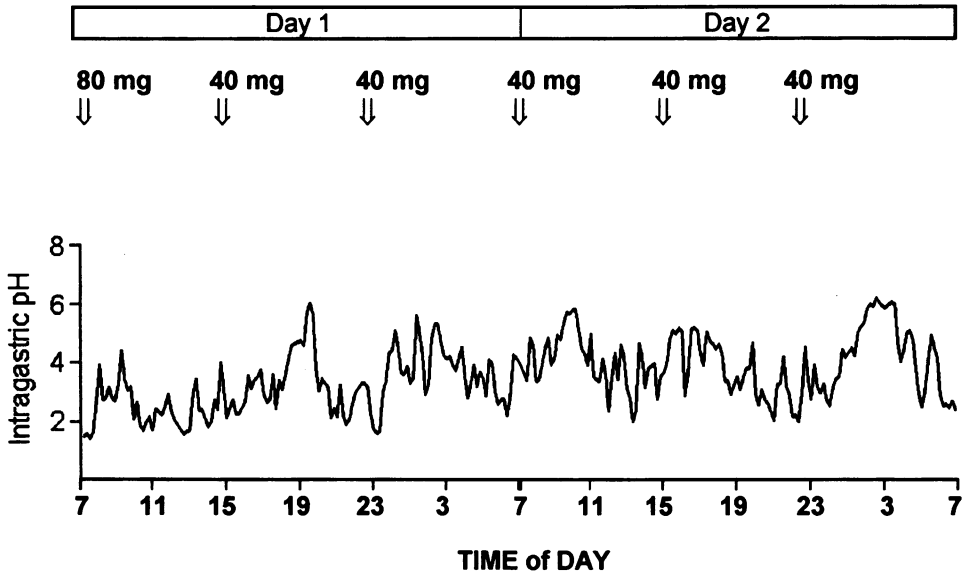

Figure 1. Median intragastric pH profile in healthy subjects (n = 6) after an initial bolus of 80 mg pantoprazole followed by eight hourly bolus doses of 40 mg pantoprazole.

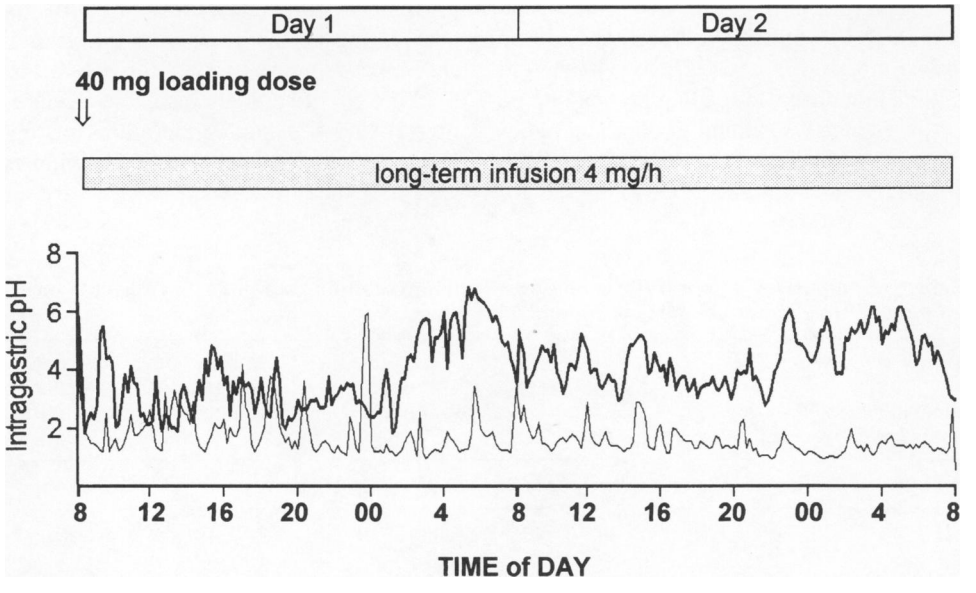

Figure 2. Median intragastric pH profile in healthy subjects receiving continuous infusion of placebo (thin line) or 40 mg bolus injection of pantoprazole followed by continuous infusion of four mg/hr pantoprazole (thick line) (n = 6).

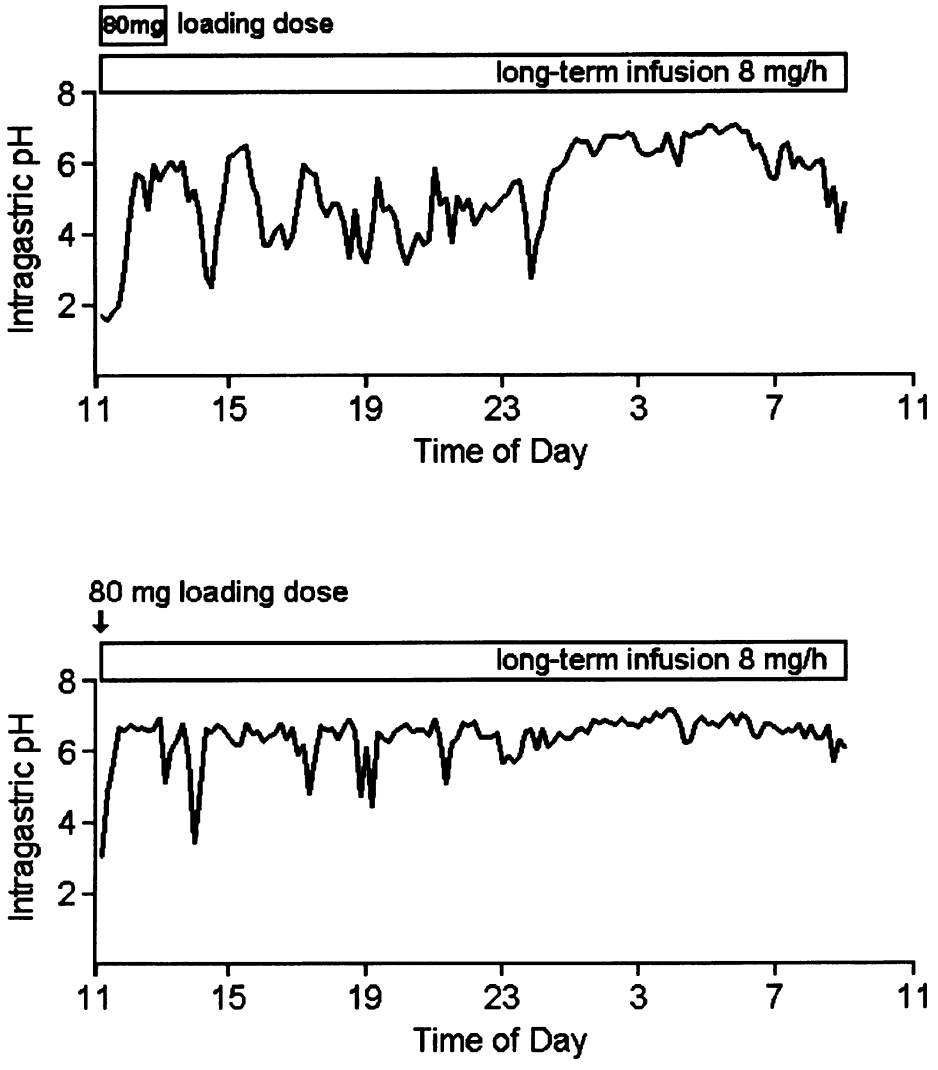

Figure 3. Median intragastric pH profile in healthy subjects (n = 8) receiving an infusion of eight mg/hr pantoprazole after an initial loading dose of 48 mg/hr pantoprazole for the first two hours or eight mg/hr pantoprazole after a rapid bolus of 80 mg pantoprazole (n = 7).

a physiological hemostasis is, therefore, a rapid bolus of 80 mg pantoprazole followed by an infusion of eight mg pantoprazole per hour.

Tolerability

Pantoprazole was well-tolerated by the subjects. No clinically significant changes in the electrocardiograms or laboratory tests were found. Adverse experiences were few and none was considered clinically important or related to drug exposure.

DISCUSSION

The results clearly show that a rapid increase of the intragastric pH above 6 can be reliably achieved only by continuous infusion with a large initial bolus dose. Spreading

the bolus over a time of two hours delays the maximum pH effect by 12 hours. With the lower infusion rate of four mg/hr, a pH above 6 is also eventually achieved. But this will take some time and therefore is not suitable for emergency application. However, this dose may well be used as a maintenance dose, once a desired intragastric pH has been reached [25]. Intermittent bolus application cannot achieve the necessary intragastric pH because proton pumps are continuously being regenerated [29]. This implies that a proton pump inhibitor should be continuously available in the circulation to inhibit newly generated pumps and thereby inhibit gastric acidity for prolonged periods. In healthy subjects the half-life of proton pump inhibitors in the circulation is approximately 60 minutes. Since it takes four half-lives for a drug to be effectively eliminated from the circulation, bolus injections would have to be given every two to three hours in order to keep sufficient drug in the circulation. Such investigations have not yet been carried out and this mode of application would appear to be very impracticable for clinical use. Currently, continuous infusion is easy to apply and to control.

These data found for pantoprazole are almost identical with those that we and other investigators have found for omeprazole [24, 25, 26]. Both drugs seem to be equivalent when given intravenously.

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