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Effects of bolus or intra venous infusion of famotidine on gastric pH in patients with duodenal ulcer disease

Duodenum ülserli hastalarda aralıklı ve perfüzyon şeklinde verilen famotidin'in mide pH'sı üzerindeki etkisi

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SUMMARY: *To compare gastric pH control using intravenous famotidine as primed, continuous infusion versus intermittent infusion.*

In a prospective study, 20 patients with uncomplicated active peptic ulcer disease were randomly assigned to receive either famotidine 10 mg bolus followed 1.67 mg/h infusion or famotidine 20 mg intravenously every 12h. Intraluminal gastric pH was recorded continuously during the 48h period using an antimony pH electrode. In the first 24h, gastric pH was recorded without therapy and in the second 24h period, patients were randomised into two groups to receive either continuous infusion or bolus famotidine therapy. pH results of the groups were compared using student's t test.

In the second 24h period, overall mean gastric pH was higher in the continuous infusion group (3.78±0.7 versus 2.41±0.6, p<0.01) and when gastric pH greater than 4 was used as an end point, the continuous infusion group exhibited better pH control (44.8±17.9%) versus 22.4±18.3% p<0.01). Also, percent of overall time above pH 5 was greater in the continuous infusion group 32.5 ± 12.7% versus 13.7 ± 14.6% p<0.003).

On the basis of both efficacy and cost, intermittent bolus injections should be replaced by continuous intravenous infusion in hospitalized patients requiring treatment with histamine H2 receptor antagonists.

Key Words: **Famotidine, pH monitoring**

ÖZET: *Aralıklı intravenöz bolus ve devamlı perfüzyon şeklinde verilen famotidin'in mide pH'sı üzerindeki etkilerinin karşılaştırılması.*

Bu prospektif çalışmaya komplikasyonsuz duodenum ülseri olan 20 hasta kabul edildi. 10 hastaya 10 mg famotidin'in intravenöz bolus enjeksiyonunu takiben 1.67 mg/saat dozunda iv famotidin infüzyonu yapılırken diğer 10 hastaya da 12 saat ara ile 20 mg famotidin intravenöz yoldan enjekte edildi. Mide pH'sı antimon elektrodlar yardımı ile 48 saat boyunca devamlı olarak kaydedildi. İlk 24 saatte herhangi bir tedavi verilmezken ikinci 24 saatlik peryodda hasta gruplarına yukarıda tarif edilen şekillerde famotidin tedavisi uygulandı. Elde edilen pH değerleri student's t testi kullanılarak karşılaştırıldı.

İkinci 24 saatlik kayıt döneminde ortalama mide pH'sı devamlı infüzyon yapılan grupta daha yüksekti (3.78 ± 0.7 ve 2.41 ± 0.06, p<0.01). pH 4 üzerinde geçen süre infüzyon yapılan grupta daha fazla bulundu (%44.8 ± 17.9 ve %21.4 ± 18.3, p<0.01). Aynı şekilde pH 5 ve üzerinde geçen süre de infüzyon yapılan grupta daha uzundu (%32.5 ± 12.7 ve %13.7 ± 14.6, p<0.003).

Yararlılık ve maliyet açısından ele alındığında, hastanede yatırılarak H2 reseptör blokeri tedavisine ihtiyaç duyulan hastalarda devamlı infüzyon şeklinde tedavi aralıklı bolus tedavisine tercih edilmelidir.

Anahtar Kelimeler: **Famotidin, pH monitorizasyonu**

H_2 receptor bloking agents, especially famotidine and ranitidine, are top selling drugs in our country. Although these agents are prescribed mainly for ambulatory patients with acid-peptic diseases, they are also frequently used in hospitalized patients because of complications associated with peptic ulcer, for instance; gastrointestinal hemorrhage and to prevent acute hemorrhagic gastritis in patients in intensive care units (1-3). A common endpoint when using these agents is the maintenance of intragastric pH at greater than 4 or 5. This is often achieved using intermittent dose of H_2 receptor antagonists. Recent data suggests that continuous infusions of these medications may be more effective than intermittent doses, with respect to this endpoint (4-7). The objective of this prospective study was to compare gastric pH control using famotidine as an intermittent intravenous bolus versus continuous intravenous infusion.

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Table 1. Demographic and biochemical information of patients

Details	*IV continuous infusion group n = 10*	*IV bolus group n = 10*
Sex		
Male	8	6
Female	2	4
Mean age (years)	42(19-64)	36(19-47)
Body mass index	21.6(20.6-21.9)	21.9(20.3-22.1)
Mean serum creatinine (mg/dl)		
Before treatm.	1.2(0.9-1.4)	1.3(0.7-1.6)
After treatm.	1.1(0.7-1.3)	1.3(0.8-1.5)
Mean serum SGPT		
Before treatm.	22(16-37)	16(13-41)
After treatm.	23(14-36)	24(13-36)

PATIENTS AND METHODS

Twenty patients with uncomplicated duodenal ulcer were accepted for the study. Written consent from all patients was taken before study enrollment. Esophagogastroduodenoscopy was performed to all patients. Patients were excluded if they had allergy to famotidine or other systemic disease, serum creatinine greater than 1.5 mg/dl, SGOT and/or SGPT greater than 45 U/l, known or suspected pregnancy, history of intraabdominal surgery with in the preceeding six months or evidence for peptic ulcer complications (bleeding, obstruction etc.). Patients were also excluded if they had taken anti-ulcer medication for at least one week before study. Demographic and some biochemical values of patients are shown in table 1.

Serum creatinine, CBC and transaminases were detected at baseline and at the completion of the study. Intragastric pH was monitored using the Zinetics digitrapper pH recorder and antimony disposable pH catheters. After the insertion of pH catheter with nasogastric routh, esophagogastric junction was detected with pulling-back method and then catheter reinserted in to the stomach with standart distance (15 cm) from esophagogastric junction in all patients. Because of the side effects of radiation, this method for catheter localisation was prefered. After the intragastric localisation of the pH catheter, it was fixed with a nasal band (Hypafix). Gastric pH values were recorded during the 48h period in all patients. In the first 24h, pH values were measured without therapy and in the second 24h period, patients were randomised to two groups to receive either famotidine 10 mg intravenously over 5 minutes followed by infusion of 1.67 mg/h (40 mg/d) or famotidine 20 mg infused in 100 cc 5%) Dextrose-water (Mediflex-Baxter) over 30 minutes at every 12h. 1600 kcal/d standart diet was given to all patients. The use of antacids, sucralfate and other drugs were prohibited during the study period.

Table 2. Findings of gastric pH measurements in bolus and continuous infusion

pH parameters	*IV Bolus*	*IV continuous infusion*	*P*
Mean gastric pH			
Before treatment	1.58±0.2	1.89±0.4	>0.05
After treatment	2.41±0.6	3.78±0.7	<0.01
Time % pH>4 (After treatment)	22.4±18.3	44.8±17.9	<0.01
% pH>5 (After treatment)	13.7±14.6	32.5±12.7	<0.003
Mean pH increase	0.83±0.71	1.89±0.46	<0.01

The overall mean gastric pH, time % greater than pH 4 and 5, frequency distribution for all the gastric pH measurements above pH values from 1 to 7 were calculated and compared between the two groups. Data are presented as means ± standart deviation. Student's t test was used for statistical analysis.

RESULTS

There was no significant difference between two groups in age, body mass index, serum creatinine and transaminases before and after the study (Table 1). pH values are shown in table 2. When the mean gastric pH values for the first 24h were compared, no significant difference resulted (1.58 ± 0.2 for the bolus group and 1.89 ± 0.4 for the continuous infusion group, $p<0.05$). In the second 24h period, the overall mean gastric pH was higher in the continuous infusion group (2.41 ± 0.6 versus 3.78 ± 0.7, $p<0.01$). When gastric pH greater than 4 was used as and endpoint, the continuous group exhibited better pH control than the bolus group (44.8 ±17.9% and 22.4±18.3% respectively, $p<0.001$). Similar results were found at the percent of time patients spent above pH 5 were 32.5 ± 12.7% and 13.7 ± 14.6% for the continuous and bolus groups respectively ($p<0.003$) (Table 2).

The frequency distribution for all the gastric pH measurements above pH values from 1 to 7 are

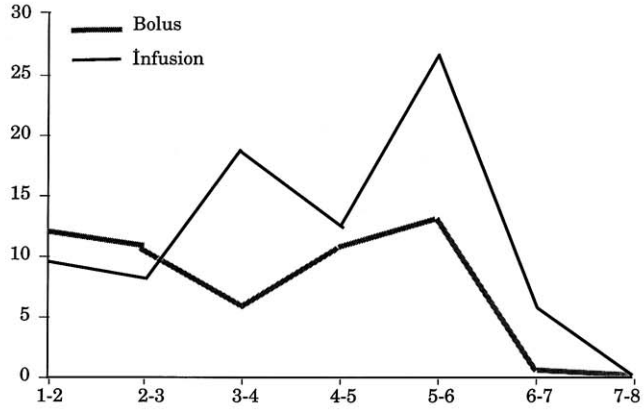

Figure 1. *Time (%) -ph curve for both bolus and intravenous influsion of famotidine*

Table 3. Frequency distribution for all gastric pH measurements in groups

pH	*time%*	
	Continuous infusion	IV Bolus group
1-2	9.4	11.7
2-3	7.6*	10.5
3-4	17.3*	5.4
4-5	11.1*	8.7
5-6	22.5*	13.1
6-7	7*	0.6
7-8	0.06	0

* = p< 0,05

shown in figure 1 and Table 3. As can be seen, the continous infusion group had a greater percentage of time between the pH 4 and 6.

DISCUSSION

Active untreated peptic ulcer disease can prove disastrous and especially gastorintestinal haemorrhage carries a substantial risk of fatal outcome despite advances in surgery and endoscopy. Clinicians have been hoping for a simple medical therapy and a non surgical therapy that reduced the frequency of bleeding or rebleeding and of surgery would be expected to decrease death rates. One possibility is antisecretory therapy but few clinical trials have had sufficient statistical power to produce a celar-cut result; some have reported significant benefits from H_2 receptor antagonists while others have no (8-13).

Initial studies showed that maintenance of the gastric pH above 3.5 with hourly antacids was more effective than placebo in preventing acute gastric mucosal lesions and gastorintestinal bleeding in patients in intensive care units (14-16,19). Subsequent reports have suggested that H_2 receptor anatgonists are as effective as antacids, easier to administer and are associated with a lower risk for aspiration pneumonia (18,19). This is the probable explanation for why H_2 receptor antagonists are used more frequently than antacids.

Although H_2 blockers are prescribed mainly for ambulatory patients with acide-peptic disease, they are frequently used to maintain the gastric pH at 3.5 or greater in patients hospitalized because of complications associated with peptic ulcer disease and to prevent acute hemorrhagic gastritis. In clinical practice, H_2 receptor antagonists were administered more frequently by bolus injection than by continous intravenous infusion. This was unanticipated because Peterson and colleagues(20) and Ostro (21) and associates reported that continuous intravenous infusion of cimetidine for 12 hours was more with elevating the gastric pH than bolus injections of equivalent doses. Watanabe et al. (7) compared the effects of intermittant famotidine (20 mg infused over 1h, every 12h) and continuous infusion (40 mg infused over 24h) in patients with peptic ulcers. They found that mean cumulative percentages of pH readings above 6 and 7 were significantly greater in the continuous infusion group. Fullarton et al. (22) were randomized the patients with acute gastrointestinal hemorrhage to receive either placebo or famotidine infusion 3.2 mg/h after a 10 mg bolus dose and they found that mean pH was 7.1 and 1.6 in the famotidine and placebo groups respectively. In the other double-blind study, patients with healed duodenal ulcer were randomised to receive placebo, famotidine 3.2 mg/h or famotidine 4 mg/h and mean 24h intragastric pH was 1.3, 6 and 6.1 in the placebo, 3.2 mg/h and 4 mg/h groups, respectively (23).

The results of our study show that continuous intravenous infusion of famotidine was significantly more effective than intermittant bolus injections. For example, mean gastric pH values during continuous intravenous infusion of 40 mg famotidine over 24h and two divided bolus dose of 20 mg famotidine every 12 hours were 3.78 and 2.41 respectively ($p<0.01$). Moreover, gastric pH values did not fluctuate widely during continuous intravenous infusion. After the bolus injection, gastric pH value was increased to pH 4 or above in 30 min. and remained as 30-320 min. (mean 175 min.) at these pH levels and than decreased to pH 2 or below immediately. For this reason, to obtain of the

constant intragastric pH values above 4 or more, intervals of intravenous bolus injections should be shorter (six times or more in 24 h). The wide variations in gastric pH after the bolus injections may be related to the fluctuations in plasma famotidine concentration. In contrast, during the continuous intravenous infusion, plasma levels of drug probably remained quite constant.

How should these findings influence the care of hospitalized patients for whom H_2 receptor antagonist therapy is prescribed ? Our study demonstrates better control of intragastric pH in patients receiving famotidine by constant infusion versus intermittent dosing. On the basis of both efficacy and cost, intermittant bolus injections should be discontinued and replaced with continuous intravenous infusions.

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