Gut, 1989, **30**, 1105–1109

Liver, biliary, and pancreas

Frequent non-response to histamine H_2-receptor antagonists in cirrhotics

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SUMMARY **The effect of ranitidine 300 mg po given at 18 00 h (famotidine 40 mg/cimetidine 800 mg) on the night time gastric pH was tested using longterm intragastric pH monitoring in 27 patients with and 32 patients without liver cirrhosis. A rise in the gastric pH above 4·0 for more than six hours between 18 00 h and 06 00 h was considered as sufficient effect (response) of the H_2-receptor antagonists on gastric acidity. Among the patients with cirrhosis, there were significantly ($p<0·005$) more non-responders to ranitidine (16 of 27 patients) than in the control group (six of 32). When 13 of the 22 non-responders to ranitidine were subsequently treated with famotidine, only two showed a sufficient rise in their gastric pH. Of the 11 patients not responding to both H_2-receptor antagonists, 10 were finally treated with cimetidine and eight did not respond. Plasma levels of all three drugs measured two and four hours after oral administration were not significantly different between cirrhotic and noncirrhotic patients as well as between responders and non-responders. In addition, in all patients plasma levels were far above the corresponding IC_{50} values. Therefore, differences in the absorption and plasma levels of these drugs cannot account for the frequent non-response in cirrhotics.**

Some peptic ulcers are resistant to adequate treatment with a histamine H_2-receptor antagonist.[1] Few of these ulcers heal after changing the H_2-antagonist. The efficacy of H_2-receptor antagonists is mainly judged by the criterion of ulcer healing – that is, only after four to eight weeks of treatment. It is generally accepted that the nocturnal suppression of gastric acid secretion is most important[2] for the therapeutic effect of the H_2-receptor antagonists. In patients with ulcers resistant to H_2-receptor antagonists, failure of acid suppression was observed.[3–5] Therefore, socalled non-responders to these agents may be identified by monitoring the gastric acidity at the beginning of the therapy. It has recently been shown that longterm intragastric pH registration is equivalent to pH measurements of gastric aspirates.[6] In contrast with the aspiration method, longterm intragastric pH monitoring does not interfere with the gastric content, the patients' mobility, their nutrition or their sleeping pattern. Thus, the current gastric pH, which is probably the most important pathophysiological factor, can be registered directly and continuously.

The incidence of peptic ulcers in patients with cirrhosis of the liver may be increased[7,8] and patients with chronic liver disease are often treated with H_2-receptor antagonists for peptic ulcer disease or other indications. Therefore, we investigated in the present study, the effect of ranitidine (subsequently that of famotidine/cimetidine in the case of non-response to ranitidine/famotidine) on the nocturnal intragastric pH in cirrhotics and a control population.

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Accepted for publication 19 December 1988.

Methods

PATIENTS

Fifty nine inpatients, 27 with cirrhosis of the liver, proven histologically and/or with typical laboratory and clinical signs (oesophageal varices, ascites) and 32 without cirrhosis (controls) were included in the present study. They all had indications for treatment

Table 1 *Summary of clinical data of studied patients*

	Cirrhotics n=27	*Controls n=32*	*p*	*Responders n=37*	*Non-responders n=22*	*p*
Age (yr) (SD)	51·6 (15·6)	58·4 (15·7)	NS	57·8 (16·9)	51·2 (13·5)	NS
Gender (m/f)	15/12	22/10	NS	25/12	12/10	NS
Body weight (kg)	68·6 (16·1)	68·8 (11·6)	NS	70·1 (12·9)	66·9 (14·7)	NS
Ascites	17	1		8	10	
Oedema	13	3		10	6	
Child classification (A/B/C)	7/12/8	–		2/6/3	5/6/5	
Alcohol/non-alcohol drinkers	17/10	16/16	NS	20/17	13/9	NS
Amount of alcohol before admission (g/d)	90·6 (49·7)	34·1 (35·8)	<0·001	48·3 (37·6)	86·2 (62·6)	NS
Smokers/non-smokers	11/16	12/20	NS	13/24	10/12	NS
Cigarettes per day	20·9 (12·0)	22·8 (15·1)	NS	21·3 (14·9)	22·6 (11·9)	NS
Cardiac insufficiency	2	5		6	1	
Renal insuffiency	6	3		5	4	
Arterial hypertension	2	6		6	2	
Diabetes mellitus	5	6		9	2	
Reflux oesophagitis	2	4		4	2	
Gastric ulcer	3	9		9	3	
Duodenal ulcer	2	6		6	2	
Erosive gastritis and bulbitis	15	11		13	13	
Prophylactic treatment	5	2		5	2	

with an H_2-antagonist, namely peptic ulcer disease, erosive gastritis and reflux oesophagitis, diagnosed by endoscopy. Clinical data of the two groups of patients are summarised in Table 1.

STUDY DESIGN

A miniaturised bipolar glass pH electrode with a combined reference electrode (model LoT 440 M4, Ingold Messtechnik AG, Urdorf, Switzerland) was used. A solid state recorder (24 h pH-monitor, Proxima SrL, Porto Mantovano, MN, Italy) was calibrated at room temperature with commercial buffer solutions of pH 7 and 4 (Beckman Instruments, Fullerton, CA, USA, pH 7·00 (0·01) and 4·00 (0·01) at 25°C). The drift of the electrodes at the end of the recording periods was lower than 0·1 pH units. The pH values were measured every six seconds and the arithmetic mean of eight successive readings was calculated and recorded.

After the patients had given informed consent, in the morning the electrode was introduced through a nostril into the gastric body (distance from the measuring tip of the electrode to the cardia about 10 cm and to the nostril 50–60 cm). The electrode cable was fixed at the nose and one of the ears and the recorder was carried by the patients in a small bag. A standard dinner was served at 17 30 h and at 18 00 h the patients received the H_2-receptor antagonist.

Blood samples were taken immediately before, two, and four hours after oral administration of the drug, and plasma levels of unchanged ranitidine,[9] famotidine,[10] and cimetidine[9] were determined by specific reverse phase HPLC methods.

An intragastric pH above 4 for more than six hours monitored from 18 00 h to 06 00 h was considered as a sufficient therapeutic effect (response). All the patients received 300 mg ranitidine initially. To the non-responders of ranitidine, famotidine 40 mg was administered and the non-responders to both H_2-blockers finally received 800 mg cimetidine. A wash-out period of at least 48 hours was kept between the various drug challenges. The patients did not receive other drugs that may have influenced the acid secretion for at least one week before the study and were not allowed to smoke, eat, or drink alcohol and coffee during the study period.

The study conformed with the 1975 Declaration of Helsinki ethical guidelines and the study protocol was approved by the local ethical committee. For statistical analysis the χ^2 test, Fisher's exact probability test, and Student's *t* test were used.

Results

In Table 1 clinical data of responders and non-responders to ranitidine are summarised. Figure 1

Table 2 *Response to ranitidine (300 mg po given at 18 00 h) in patients with and without liver cirrhosis. Gastric pH higher than four for more than 50% of time from 18 00 h to 06 00 h was regarded as response*

	Responders	*Non-responders*	*n*
Cirrhotics	11	16	27
Controls	26	6	32
n	37	22	59

Fisher's exact test: p<0·005.

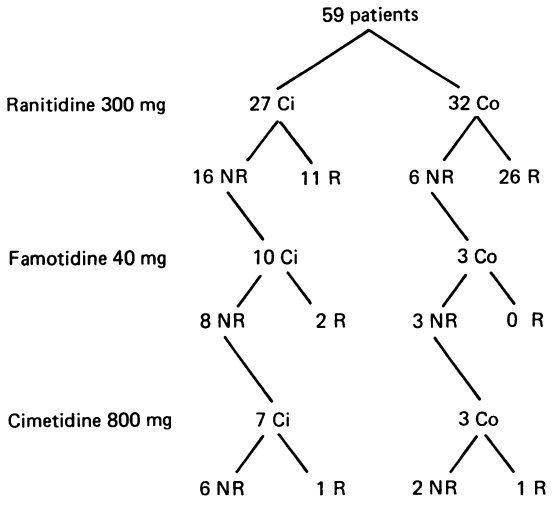

Fig. 1 *Flow diagram of treatment with H_2-receptor antagonists in cirrhotic patients (Ci) and controls (Co) exhibiting response (R) or non-response (NR) to the drugs.*

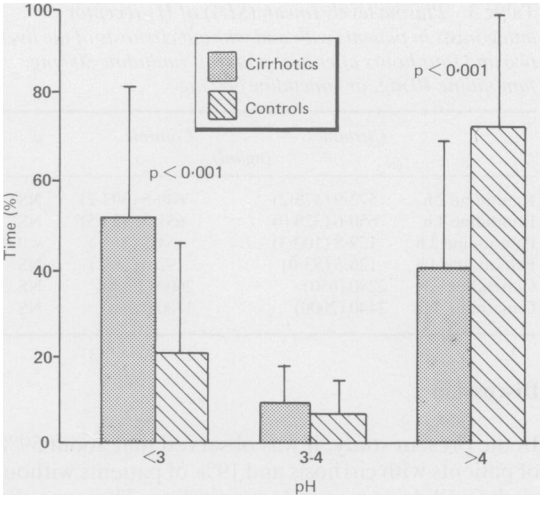

Fig. 2 *Ranges of the intragastric pH-values as expressed in percentages of time periods in cirrhotics and controls after an oral dose of 300 mg ranitidine.*

shows the treatment response to the different H_2-antagonists tested. Of 27 cirrhotics and 32 controls, 16 and six, respectively, did not respond to 300 mg po ranitidine. The difference in response between both groups was statistically significant ($p<0·005$). When 10 of the cirrhotic non-responders and three of the non-cirrhotic non-responders were treated with 40 mgpo famotidine eight and three patients did not respond respectively. When seven of the cirrhotic non-responders to famotidine and the three controls were finally treated with 800 mg po cimetidine only one responded in each group (Fig. 1).

The means (SD) of the percentages of time with gastric pH after ranitidine administration above 4, between 3 and 4 and below 3 from 18 00 h to 06 00 h are shown in Figure 2. In cirrhotics 39·3 (29·9)% and in non-cirrhotics 72·6 (26·1) of the measured time, the pH was above 4. On the other hand, the intragastric pH was below 3 in cirrhotics and non-cirrhotics respectively 51·3 (30·4)% and 20·7 (25·1)% of time (Fig. 2). In both cases the difference was statistically significant ($p<0·001$).

The hourly mean intragastric pH-values (SD) from 12 00 to 06 00 next morning in cirrhotics and controls are shown in Figure 3. In contrast with the controls in the cirrhotic group there was only a minor and delayed increase in the pH-profile after the administration of 300 mg ranitidine at 18 00.

In the prestudy plasma samples H_2-receptor antagonist levels were not detectable. The plasma levels of all three H_2-receptor antagonists two and four hours after oral intake were in the therapeutic range and were not significantly different between cirrhotic patients and patients without cirrhosis (Table 3). Likewise, the plasma levels of ranitidine in responders and non-responders (593·8 (394·5) ng/ml *v* 634·2 (493·1) after two hours and 606·4 (409·4) *v* 697·8 (331·8) after four hours) were not significantly different.

Factors such as smoking, alcohol consumption, pretreatment with H_2-blockers, other major diseases, Child grade, ascites, oedema, oesophageal varices, age, weight and gender (Table 1) had no significant influence on the response to ranitidine treatment.

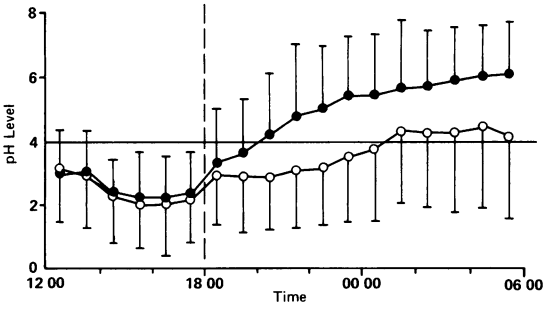

Fig. 3 *Hourly mean intragastric pH-values (SD) of cirrhotics ○——○ and controls ●——●. All patients received an oral dose of 300 mg ranitidine at 18 00. The differences between the mean pH-values of cirrhotics and controls are statistically significant ($p<0·05$) from 20 00 to 06 00.*

Table 3 *Plasma levels (mean (SD)) of H_2-receptor antagonists in patients with and without cirrhosis of the liver two and four hours after oral intake of ranitidine 300 mg, famotidine 40 mg, or cimetidine 800 mg*

	Cirrhotics	*Controls*	*p*
	(ng/ml)		
Ranitidine 2 h	572·9 (473·2)	640·5 (393·2)	NS
Ranitidine 4 h	650·6 (328·0)	631·5 (429·5)	NS
Famotidine 2 h	129·8 (100·3)	54·8 (35·1)	<0·06
Famotidine 4 h	126·5 (83·0)	92·0 (68·2)	NS
Cimetidine 2 h	2280 (650)	2600 (1500)	NS
Cimetidine 4 h	2440 (2000)	1700 (1200)	NS

Discussion

In the present study, it was observed that about 59% of patients with cirrhosis and 19% of patients without cirrhosis did not respond to ranitidine. There may be differences in the individual or general response[11] to various H_2-receptor antagonists when given in equipotent doses. In terms of intragastric acidity, however, most of our non-responders to ranitidine showed no sufficient response when treated subsequently with famotidine and cimetidine.

In one non-responder to all three H_2-blockers, the pH monitoring could be repeated after six months after administration of 300 mg po ranitidine and similar results were obtained again. In addition, five non-responders to all three H_2-receptor antagonists were treated with higher doses. Three received 900 mg ranitidine and two 80 mg famotidine. Only in one female patient of the control group a sufficient response to the three-fold higher dose of ranitidine was observed. This would support the concept of a general impairment in the response to H_2-receptor antagonists.

Young *et al*[12] reported that the bioavailability of ranitidine in cirrhotic patients was increased because of impaired hepatic and renal clearance which was not confirmed by others.[13,14] In our patients with cirrhosis, plasma levels not only of ranitidine, but also those of famotidine and cimetidine, four hours after oral intake were higher (although not significantly different), than in the control group.

A less reliable oral absorption of the drugs soon after dinner in both groups may not contribute to the high failure rate as a longer duration of intragastric pH above 3·5 (about 10 *v* 7 hours) was reported when 300 mg ranitidine or 40 mg famotidine was given immediately after dinner rather than three hours after dinner in healthy volunteers.[15] In addition, as reported earlier,[3,4] the plasma levels of the H_2-receptor antagonists were similar in our responders as well as non-responders, indicating that the failure was not caused by ineffective drug concentrations. Therefore, delayed or impaired gastrointestinal absorption can be ruled out as a causative factor for non-response particularly for the high non-responder rate in cirrhotics.

The reasons for the non-response to H_2-receptor antagonists in some patients (and the more frequent non-response in cirrhotics) are not known yet. So far there were no reports on testing acid suppression by H_2-receptor blockers in cirrhosis. Possible explanations for the non-response in these patients could be changes in the number and/or sensitivity of the H_2-receptors of the gastric parietal cells, competitive stimulation of the receptors by auto-antibodies[16] or other yet unknown substances, stimulation of the acid secretion by other mechanisms, such as excessive vagal drive[17] or diminished prostaglandin content in gastric mucosa as reported in patients with cirrhosis.[18] In addition, increased plasma histamine levels, which might increase gastric acid secretion, were reported in cirrhosis.[19,20] According to a recent report, the serum gastrin levels are lower in patients with cirrhosis than in normal controls.[21] The gastric acid output, however, was found to be normal[8,18,21] or even decreased.[22,23]

Clinical or laboratory data, not related to cirrhosis, which might explain the (non-)response to the H_2-antagonists were similar between the two groups and thus could not account for the observed differences. Possible disturbances, such as dislocation of the electrode (into the duodenum or the oesophagus), alkaline duodenal-gastric reflux, repeated eating and drinking, and hypochlorhydria, which might result in an apparent acid suppression would operate in favour of a raised pH in both groups and consequently cannot account for the higher failure rate in cirrhotics.

Smoking and alcohol may interfere with the effect of H_2-antagonists. In healthy volunteers Bauerfeind *et al*[24] found that ranitidine and cimetidine were less potent in smokers than in non-smokers. In our present study, smoking habits of the two groups before admission did not differ and it is very unlikely that the patients with cirrhosis of the liver have more often smoked secretly and that this factor would have a confounding influence on our results.

As expected, alcohol intake before admission was significantly higher in cirrhotics than in non-cirrhotics, but was not significantly different between responders and non-responders. Therefore, this cannot explain the higher rate of non-response in the cirrhotic group. The effect of alcohol on gastric acid secretion is minor, mainly depending on the amount, concentration of alcohol and type of beverage.[25]

According to a study of Koop *et al*[26] patients with severe reflux oesophagitis can show an impaired response to ranitidine. As in four of our six patients

with reflux oesophagitis a sufficient increase of the intragastric pH was recorded, this cannot explain our results.

In conclusion, we consider that despite sufficient plasma levels the incidence of non-response to histamine H_2-receptor antagonists is higher in patients with cirrhosis of the liver.

We wish to thank the medical and nursing staff of the Department of Gastroenterology. Parts of the results were presented at the 4th Meeting of the German Association for the Study of the Liver (GASL) Berlin, January 1988 and the 29th Spring Meeting of the German Society of Pharmacology and Toxicology, Mainz, March 1988.

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