Does smoking interfere with the effect of histamine H$_2$-receptor antagonists on intragastric acidity in man?

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SUMMARY The interaction between smoking and the effect of histamine H$_2$-antagonists on intragastric acidity was examined in a double blind double dummy placebo controlled study. Healthy volunteers, 11 smokers and 10 non-smokers, were given, on four separate days at least one week apart, either placebo or cimetidine 800 mg nocte or ranitidine 2×150 mg per day or ranitidine 300 mg nocte. Tablets were taken at 2115 and 0900 h. Smokers smoked a cigarette hourly from 0700 to 2300 h. Breakfast, lunch, and dinner were standardised. Intragastric acidity was measured with a combined intragastric glass electrode and a solid state recorder. The subjects were fully ambulatory. The three histamine H$_2$-receptor antagonist regimens were less effective (p=0·04) in smokers than in non-smokers, but the difference between acidity of smokers and non-smokers was small. Means of medians of pH during a 24-h period with placebo, cimetidine 800 mg, raniditine 2×150 mg and ranitidine 300 mg were 1·6, 2·3, 3·1, and 2·7 in smokers and 1·5, 2·7, 3·2, and 3·1 in non-smokers, respectively. In a second part of the study seven chronic smokers were reexamined after acutely stopping smoking: inhibition of gastric acidity by histamine H$_2$-receptor antagonists was similar before and after withdrawal. Smoking does not affect intragastric acidity in untreated volunteers and only slightly decreases the effectiveness of histamine H$_2$-receptor antagonists on intragastric acidity. This effect best in part explains the unfavourable effect of smoking on healing of peptic ulcer in patients treated with these drugs.

Smoking has an unfavourable effect on the course of peptic ulcer. It may slow down healing, favour relapse, diminish the effectiveness of histamine H$_2$-receptor antagonists in duodenal ulcer[1-22] and possibly also in gastric ulcer.[23 24] The mechanism is unknown. It has been hypothesised that smoking interferes with the antisecretory effect of histamine H$_2$-receptor antagonists,[25] but the data to support this hypothesis are scanty[25] and controversial.[26 27] It is not even known if smoking affects gastric acidity.[28-37] In order to clarify the effect of smoking on intragastric acidity, we undertook a double blind crossover trial in healthy volunteers.

Methods

SUBJECTS

The studies were done in two groups of healthy

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volunteers. Eleven smokers (seven women, mean age 24 years, range 19–37 years) and 10 non-smokers (six women, mean age 25 years, range 19–30 years) agreed to participate. The mean body weight was smokers: 66 kg (range 52–79), non-smokers: 62 kg (range 45–89). Smokers were those who had been smoking at least 10 cigarettes every day for at least one year. Non-smokers had not been smoking at all before. None of the volunteers had a history of gastrointestinal diseases or was taking other drugs. Each volunteer was completed a 'Freiburg personality inventory' (FPI), a modified neuroticism-extroversion-test.[38] Twelve different FPI-scores were evaluated in smokers and non-smokers, but no differences between the two groups could be detected. Care was taken to include only subjects who tolerated the procedure well and did not experience discomfort or nausea while smoking or at night. All slept well, ate their standardised meals completely and followed their usual activities on the study days. Seven of the 11 smokers agreed to participate in

a crossover study with multiple acute withdrawals of smoking. Informed consent was given. The trial was approved by the hospital ethics committee.

STUDY SCHEDULE AND MEDICATION

Each volunteer received on four separate days at least one week apart either placebo (P), or cimetidine 800 mg nocte (Cim 800), or ranitidine 300 mg nocte (Ran 300), or ranitidine 2×150 mg per day (Ran 150) in a sequential random order. The study was conducted in a double blind fashion using a double dummy tablet technique. In the first part of the study, smokers smoked hourly one cigarette amounting to a total of 17 cigarettes per day. Non-smokers did not smoke. In the second part of the study seven smokers were reexamined 24 hours after stopping smoking.

EXPERIMENTAL DESIGN

The time course of the experiment is given in Figure 1. On the study day the volunteers started to fast at 1200 h and were admitted to our laboratory before 1600 h. A pH electrode was placed through the nares in the gastric body. The position of the electrode was verified fluoroscopically. The volunteers received the medication and a pack containing four standardised meals for the following 24 hours. Composition and energy content of the meals are given in Table 1. Water and unsweetened tea were allowed *ad libitum*. The subjects were given a diary card in which times of meals, medication and time of smoking of cigarettes was specified. The volunteers were also asked to record their daily activities, pain, hunger, sleep and fluid intake. The subjects were fully ambulatory. They returned to the hospital at 2300 h for collection of a blood sample for the measurement of carboxy-haemoglobin, cimitedine, and ranitidine. At 1600 h next day, the pH-electrode was removed and a second blood sample was taken.

pH MONITORING

pH monitoring was done as described previously.[39] A miniaturised bipolar glass electrode with a combined reference electrode (model 440 M4, Dr Ingold AG, Urdorf, Switzerland) was used. The diameter of the electrode was 4 mm, it was mounted on a polyvinyl tube with an outer diameter of 3 mm. The reference electrode was situated 3 cm proximally to the glass

Table 1   Composition of standard meals

Breakfast (0700 hours) 2896 kJ	180 g yoghurt 100 g bread + 20 g butter 30 g marmalade 2 cups of coffee with milk
Lunch (1200 hours) 2911 kJ	60 g bread + 10 g butter + 50 g ham 385 g 'Bircher musli' 200 ml soup
Dinner (1800 hours) 2534 kJ	100 g bread + 20 g butter 40 g cheese + 40 g ham
Late evening snack (2100 hours) 309 kJ	1 apple
Total	8650 kJ

electrode. The recorder was calibrated according properties of the electrode at room temperature with commercial buffer solutions at pH 7·00, pH 4·01, and pH1·69 (W. Ingold AG, Urdorf, Switzerland) at the beginning and the end of each test.

RECORDER

A solid state recorder with an 18 k byte memory microprocessor was used (CM 18pH, Dr Ingold AG, Urdorf, Switzerland). pH values were measured continously at a frequency of 4 Hz. The arithmetic mean of 20 successive readings was calculated and recorded. Thus 17 280 pH values were recorded in 24 h.

PLACEMENT OF THE ELECTRODE

The electrode was introduced through a locally anaesthetised nostril and positioned in the gastric body under fluoroscopic control. The distance of the electrode tip to the nares was recorded and kept constant in subsequent tests on each subject. The electrode cable was fixed to the cheek and connected with the solid-state recorder which was carried by the subject in a bag.

ASSESSMENT OF COMPLIANCE

Compliance of the volunteers was monitored by measuring blood or serum of carboxyhaemoglobin, ranitidine and cimetidine. Carboxyhaemoglobin was measured in blood samples taken at 2300 h and 1600 h using a CO-oxymeter (Radiometer). Blood levels of cimetidine and ranitidine were measured using a high pressure liquid chromatography.[40 41]

STATISTICAL ANALYSIS

Smoothed pH time curves were constructed by kernel estimation.[42 43] From the smoothed curves the following characteristics were calculated: the time of onset of action of a drug was defined to occur when pH rose above 3·5 after administration of the drug and the rate of increase was maximal. An analysis of
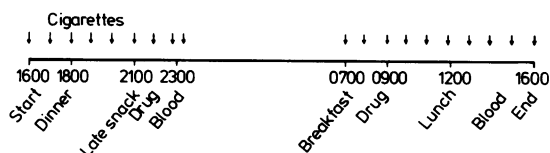
Cigarettes

Fig. 1   Time course of the 24-hour pH-metry.

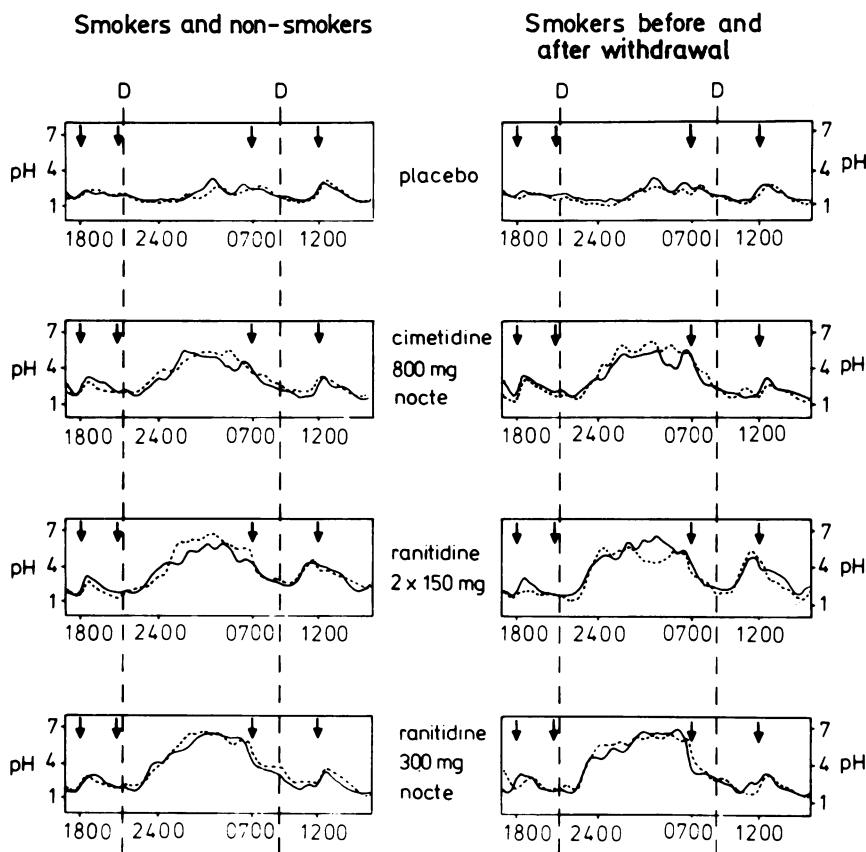Smokers and non-smokers   Smokers before and
after withdrawal

Fig. 2   *Sample averages of pH curves with placebo, cimetidine 800 mg nocte, ranitidine 2×150 mg and ranitidine 300 mg nocte. Left column: smokers (——) v non-smokers (— — — —), right column: smokers smoking (——) v smokers not smoking (24 hours after the last cigarette) (— — — —), ↓ =meals, D=drugs.*

placebo curves had previously shown that spontaneous peaks of pH above 3·5 did not occur.[39] The end of a drug effect was the time with a maximum rate of decrease of pH during the period when pH fell below 3·5. Latency was the time period between drug intake and onset. Duration of action was defined as the time between onset and the end of the effect. The intensity of secretory inhibition was the median pH between onset and end of the effect. The area under the pH curve was calculated by multiplying intensity and duration.

Median pH values were calculated for the entire 24 h period, night (2100–0700 h) and day (0700–1600 h). Overall median pH, duration, intensity, area under the curve and latency were introduced into analyses of variance for repeated measurements (ANOVA).[44] These analyses tested the effect of drugs ('drug factor'), the effect of smoking ('smoking factor'), and the interaction between smoking and a drug ('interaction term'). Other statistical tests such as χ^2 tests with Yates' correction and Mann-Whitney-U

tests were used where appropriate. Median pH values were selected for analysis; mean pH values and means and medians of H⁺ acitivities were not normally distributed.

The smallest number of volunteers needed for this study was calculated prospectively. In our previous pH-studies the standard deviation was below 0·4 pH units when means of medians of 24 hour pH values were calculated. By including more than five volunteers we should be able at least to detect a difference of 0·4 pH units. These calculations were based on an α of 0·5 and a 1-β of 0·8.[45] In case some smokers were not able to refrain from smoking in the crossover study we recruited 11 smokers and matched them with 10 non-smokers.

Results

24 HOUR INTRAGASTRIC ACIDITY WITH PLACEBO
The time course of intragastric acidity during the various treatments is shown in Figure 2. Intragastric

pH exhibited a characteristic circadian rhythm. In each individual lunch and dinner was associated with raised intragastric pH. The mean curve clearly shows the effect of lunch; the effect of dinner was less pronounced. pH rose during the night, particularly between 0200 h and 0700 h; breakfast did not lead to an additional rise of intragastric pH.

24 HOUR pH INTRAGASTRIC ACIDITY WITH HISTAMINE H₂-RECEPTOR ANTAGONISTS

Intragastric acidity during treatment with Cim 800, Ran 150 or Ran 300 showed a circadian pattern which was similar in smokers, non-smokers and smokers after stopping smoking both with cimetidine and ranitidine. All three regimes raised the nocturnal pH. The effectiveness of Cim 800, Ran 300, and Ran 150 over a 24 hour period is given in Table 2 for the first part of the study and in Table 3 for the crossover part;

the least effective regimen was cim 800 (p=0·04 ANOVA).

The values for latency, duration of action, intensity of action and area under the curve are given in Table 4. With respect to intensity and area under the curve, cimetidine was less effective than ranitidine.

INTERACTION OF DRUG EFFECT AND SMOKING

The pH curves of smokers, non-smokers and smokers after withdrawal from smoking are shown in Figure 2. Overall, the pH-curves of smokers and non-smokers and of smokers and smokers who stopped smoking were similar. In an analysis of variance (Table 3) there was a statistically significant difference (p=0·04) between pH values of smokers and non-smokers. When on the other hand separate calculations were done for daytime and night time, no difference between smokers and non-smokers, or
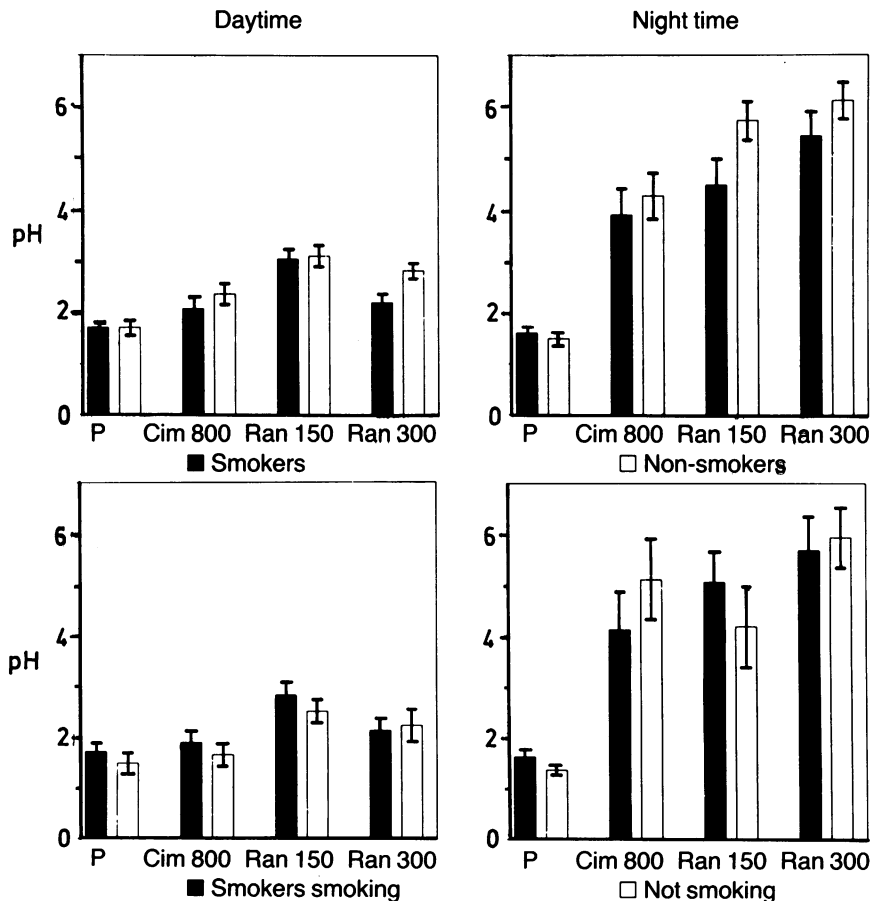

Fig. 3 *Intragastric acidity during night time (2100–0700 h) (left side) and daytime (0700–1600 h) (right side) in smokers v non-smokers (upper graphs) and smokers smoking v smokers not smoking (lower graphs). Means of individual medians (±SEM) are given. Results of ANOVA: smokers v non-smokers: night time: p=0·14, daytime: p=0·12; smokers smoking v smokers not smoking: night time: p=0·71, daytime: p=0·37.*

Table 2   *24 hour pH values (means of individual medians ± SEM) of 11 smokers and 10 non-smokers*

	Smokers	Non-smokers
P	1·6±0·09	1·5±0·09
Cim 800	2·3±0·17	2·7±0·17
Ran 300	2·7±0·19	3·1±0·17
Ran 150	3·1±0·21	3·2±0·13

Results of analysis of variance (ANOVA): (placebo values not included)

Drug factor	F=6·71
	p=0·003
Smoking factor	F=4·68
	p=0·04
Interaction term	F=0·53
	p=0·59

Contrasts (differences between two drugs as apriori specified):

Ranitidine 300 mg v ranitidine 2×150 mg	F=2·15
	p=0·14
Ranitidine 300 mg v cimetidine 800 mg	F=4·74
	p=0·04

Drug factor is the difference between the three regimens regardless of cigarette consumption. Smoking factor is the difference between smokers and non-smokers regardless of the drug taken. Interaction term is the difference between smokers and non-smokers in relation to the different drugs.

Table 3   *24 hour pH values (means of individual medians ± SEM) of seven smokers before and after withdrawal*

	Before stopping	After stopping
P	1·6±0·12	1·4±0·11
Cim 800	2·2±0·22	2·1±0·33
Ran 300	2·6±0·26	2·8±0·32
Ran 150	3·1±0·29	2·8±0·39

Results of analysis of variance (ANOVA): (placebo values not included)

Drug factor	F=4·23
	p=0·04
Smoking factor	F=0·14
	p=0·72
Interaction term	F=0·51
	p=0·61

Drug factor, smoking factor, and interaction term are explained in Table 3.

smokers before and after they stopped smoking was obtained; this is illustrated in Figure 3. Furthermore, acutely stopping smoking did not affect the effect of histamine H$_2$-antagonists (ANOVA, Table 3). Duration, latency, intensity and area under the curve after administration of histamine H$_2$-receptor antagonists were not affected by smoking (Table 4).

COMPLIANCE, DRUG AND CARBOXYHAEMOGLOBIN SERUM LEVELS

Serum ranitidine concentrations were in the therapeutic range in all subjects taking ranitidine, serum cimetidine concentrations in all subjects taking cimetidine, and carboxyhaemoglobin was raised in all

smoking subjects. There was no overlap of carboxyhaemoglobin concentrations between smokers and non-smokers. Serum drug concentrations were equal in smokers, non-smokers and smokers after withdrawal from smoking (Mann-Whitney-U test). Mean values are shown in Table 5.

Discussion

In the present study we were unable to observe an effect of smoking on spontaneous intragastric acidity. As in our previous studies using intragastric pH-metry, there was a characteristic circadian pattern of intragastric pH.[39][46] This pattern was similar in smokers and in non-smokers. In addition, the smokers maintained this pattern after acutely stopping smoking.

So far the effect of smoking on intragastric acidity and gastric secretion has not been satisfactorily determined. The first studies on this subject either

Table 4   *Latency, duration of action, intensity of the effect on intragastric pH and area under the curve (AUC) of the pH (means ± SEM), definitions see Methods*

	Latency (h)		Duration (h)		Intensity (median pH)		AUC (units)	
	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers
Cim 800	3·1 (±0·48)	2·9 (±0·36)	6·1 (±0·31)	5·9 (±0·33)	5·2 (±0·39)	5·5 (±0·54)	32 (±3·8)	32 (±4·1)
Ran 150	3·0 (±0·48)	2·5 (±0·42)	6·3 (±0·41)	6·9 (±0·34)	6·1 (±0·34)	6·2 (±0·21)	38 (±4·0)	44 (±2·9)
Ran 300	2·6 (±0·37)	3·0 (±0·38)	6·8 (±0·30)	6·3 (±0·32)	6·5 (±0·26)	6·6 (±0·08)	45 (±3·5)	42 (±3·0)

Results of analysis of variance (ANOVA):

Smoking factor	F=0·07		F=0·01		F=0·72		F=0·08	
	p=0·80		p=0·91		p=0·20		p=0·80	
Drug factor	F=0·38		F=1·35		F=9·90		F=11·14	
	p=0·69		p=0·27		p=0·0003		p=0·0002	
Interaction term	F=1·08		F=0·90		F=0·07		F=1·32	
	p=0·35		p=0·41		p=0·93		p=0·28	

Drug factor, smoking factor, and interaction term are explained in Table 3.

Table 5 Blood concentrations at 2300 h of carboxyhaemoglobin (HbCO), cimetidine and ranitidine (means±SEM). HbCO was higher in smokers than in non-smokers (Mann-Whitney-U, p<0·001), and fell in smokers after stopping smoking (WS) to control values (Mann-Whitney-U, p<0·01)

Comparison between smokers (n=11) and non-smokers (n=10)

	Smokers	Non-smokers
HbCO (% of total Hb)	5·5 (±1·2)	1·9 (±0·5)
Ran 300 (ng/ml)	483·0 (±170)	432·0 (±310)
Ran 150 (ng/ml)	325·0 (±150)	217·0 (±92)
Cim 800 (µg/ml)	2·5 (±1·0)	1·8 (±0·8)

Crossover comparison between smokers (n=7) before and after stopping smoking

	Before stopping	After stopping
HbCO (% of total Hb)	5·5 (±0·6)	1·5 (±0·4)
Ran 300 (ng/ml)	515·0 (±65)	742·0 (±167)
Ran 150 (ng/ml)	355·0 (±63)	240·0 (±140)
Cim 800 (µg/ml)	2·7 (±0·4)	2·5 (±0·9)

showed an increase of gastric acidity by smoking in healthy controls and ulcer patients,[35] or no consistent effect.[32] In more recent studies gastric acidity or gastric acid output were examined: either no effect,[29-31 33] or a decrease,[36] or stimulation,[37 47] or inhibition followed by stimulation[34] were reported. These studies were not adequately controlled, smoking was not standardised, the effect of smoking was only assessed during short periods of a few hours or it was not even mentioned if the smokers smoked during the study, or whether the gastric tube or smoking after intubation caused discomfort or nausea. Gastric acidity was assessed by intermittent gastric aspiration which may on its own affect gastric secretion[48 49] and therefore may lead to artefacts. In the present study smoking was standardised, smokers were compared with non-smokers and served, in the crossover part of the study, as their own controls after stopping smoking. Smokers stopped smoking 24 hours before repeating the study. This period is long enough to reduce nicotine levels in the plasma to values of non-smokers.[50] Intragastric acidity was assessed by continuous standardised 24-hour pH-metry, which has been validated previously and shown to be reliable.[39] All subjects were well adapted to this method.

We observed that smoking interfered with the effect of histamine H_2-receptor antagonists on intragastric acidity. Ranitidine and cimetidine were less potent in smokers than in non-smokers. The difference between smokers and non-smokers, although statistically significant, however, was slight and amounted to less than half of a pH unit. Ranitidine and cimetidine were highly effective in non-smokers as well as in smokers. As in previous studies,

ranitidine had a more pronounced antisecretory effect than cimetidine.[39 51]

It has been suggested by Boyd, et al[25] that the unfavourable effect of smoking in duodenal ulcer patients is caused by direct interference between smoking and histamine H_2-receptor antagonists: thus, smoking would decrease the antisecretory effect of H_2-receptor antagonists, possibly by accelerating gastric emptying and thus altering the pharmacokinetics of these drugs.[52] The data of these studies are difficult to interpret. The number of subjects examined was small, the drugs were given in an uncontrolled manner and nocturnal acidity was determined by intermittent gastric aspiration.[25] Other authors were either unable to observe an interaction of smoking and histamine H_2-receptor antagonists[26 28] or they observed such an effect only under special conditions, such as after giving a low dose of these drugs. In addition, the analysis of data was inadequate.[27] None of the studies fulfilled the postulate of an adequate control of smoking, a double blind administration of the drug and a continuous and long term measurement of intragastric pH. The present studies were carried out in healthy volunteers because several 24 h measurements of pH over several weeks were necessary. In patients with duodenal ulcer studies of this type are difficult because acid secretion may fall after ulcer healing and rise again at the time of a recurrence;[53] thus, stable conditions would not be maintained. Also, it has recently been shown that duodenal ulcer patients react to ranitidine and cimetidine similarly to healthy controls when intragastric acidity is measured by our technique (H Merki and L Witzel, personal communication). Therefore, it may be postulated that ulcer patients respond to smoking in a similar way as healthy controls. As smoking has no effect on gastric acidity in untreated subjects and has only a small effect on the inhibition of intragastric acidity by histamine H_2-receptor antagonists, it is likely that the unfavourable effects of smoking on ulcer healing are mediated by factors other than acid secretion. For example, smoking may increase duodenogastric reflux,[54] accelerate gastric emptying of liquids[55] and slow gastric emptying of solids.[56 57] Effects of smoking on bicarbonate secretion[58-62] gastric mucosal blood flow[63 64] and prostaglandin synthesis[66 67] are not yet settled. Smoking also may change drug metabolism.[68] In the present study serum drug concentrations were determined for the purpose of assessing compliance of the volunteers; multiple sampling was therefore not done. It is unlikely, however, from our data that smoking has a major effect on drug serum concentrations. Additional studies are necessary to clarify this point.

In conclusion, we have shown that smoking does

not affect intragastric acidity of healthy untreated man. Smoking interferes with the antisecretory effect of histamine H₂-receptor antagonists, but only to a minor degree.

References

1 Sonnenberg A, Mueller-Lissner SA, Vogel E, *et al.* Predictors of duodenal ulcer healing and relapse. *Gastroenterology* 1981; **81**: 1061–67.

2 Gugler R, Rohner HG, Kratochvil P, Brandstatter G, Schmitz H. Effect of smoking on duodenal ulcer healing with cimetidine and oxmetidine. *Gut* 1982; **23**: 866–71.

3 Korman MG, Hansky J, Eaves ER, Schmidt GT. Cigarette smoking and the healing of duodenal ulcer. [Abstract] *Gastroenterology* 1982; **82**: 1104.

4 Korman MG, Shaw RG, Hansky J, Schmidt GT, Stern AI. Influence of smoking on healing rate of duodenal ulcer in response to cimetidine or high-dose antacid. *Gastroenterology* 1981; **80**: 1451–3.

5 Korman MG, Hansky J, Eaves ER, Schmidt GT. Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. *Gastroenterology* 1983; **85**: 871–4.

6 Ireland A, Gear P, Colin-Jones DG, Golding PL. Ranitidine 150 mg twice daily VS 300 mg Nightly in Treatment of Duodenal Ulcers. *Lancet* 1984; **ii**: 274–5.

7 Lam SK, Koo J. Accurate prediction of duodenal-ulcer healing rate by discriminant analysis. *Gastroenterology* 1983; **85**: 403–12.

8 Hetzel DJ, Korman MG, Hansky J, *et al.* The influence of smoking on the healing of duodenal ulcer treated with oxmetidine or cimetidine. *Aust NZ J Med* 1983; **13**: 587–90.

9 Lee FI, Costello FT, Fielding JD. Ranitidine compared with cimetidine in the short-term healing of duodenal ulcer. *Postgrad Med J* 1983; **59**: 88–92.

10 Manousos ON, Zografos A, Nicolaou A, Scandalis N, Kalogerakou-Ioannidi E. A double-blind study of cimetidine in patients with duodenal or gastric ulcer in Greece. *J Int Med Res* 1978; **6**: 381–3.

11 Lee FI, Samloff MI, Hardmann M. Comparison of tripotassium di-citrato bismuthate tablets with ranitidine in healing and relapse of duodenal ulcer. *Lancet* 1985; **i**: 1299–301.

12 Kang JY, Piper DW. Cimetidine and colloidal bismuth in treatment of chronic duodenal ulcer. Comparison of initial healing and recurrence after healing. *Digestion* 1982; **23**: 73–9.

13 Moshal MG, Spitaels JM, Khan F, Mason J, Naidoo V, Schlemmer L. Factors affecting duodenal ulcer healing. Four double-blind trials in 193 patients. *S Afr Med J* 1982; **61**: 202–6.

14 Aenishänslin W, Bärlocher C, Bernoulli R, *et al.* Misoprostol und Cimetitin bei der Behandlung des

Ulcus duodeni. *Schweiz med Wochenschr* 1985; **115**: 1225–31.

15 Bianchi Porro G, Prada A, Petrillo M, Lazzaroni M. Gastric acid secretion, smoke and duodenal ulcer healing. [Letter] *Gastroenterology* 1982; **82**: 394–5.

16 Barakat MH, Menon KN, Badawi AR. Cigarette smoking and duodenal ulcer healing. An endoscopic study of 197 patients. *Digestion* 1984; **29**: 85–90.

17 Adami HO, Bjorklund O, Enander LK, *et al.* Cimetidine or propantheline combined with antacid therapy for short-term treatment of duodenal ulcer. *Dig Dis Sci* 1982; **27**: 388–93.

18 Classen M, Dammann HG, Domschke W, *et al.* Kurzzeit-Therapie des Ulcus duodeni mit Omeprazol und Ranitidin. *Dtsch med Wochenschr* 1985; **110**: 210–5.

19 Barr GD, Paris CH, Middleton WRJ, Piper DW. Comparison of ranitidine and cimetidine in duodenal ulcer healing. *Med J Aust* 1982; **2**: 83–5.

20 Bianchi Porro G, Burland WL, Hawkins BW, *et al.* Long-term treatment of duodenal ulcer with cimetidine: a review H2-receptor antagonists. Amsterdam: Excerpta Medica, 1979.

21 Aenishänslin W, Bergoz R, Capitaine Y, *et al.* Ranitidintherapie des Ulcus duodeni: Vergleich der zweimaligen Applikation und der einmaligen Applikation. *Schweiz Med Wochenschr* 1986; **116**: 637–41.

22 Bertschinger PH, Lacher G, Aenishänslin W. Presenting characteristics of patients with duodenal ulcer and outcome of medical treatment: myths, hypothesis and facts. *Digestion* (in press).

23 Kellow JE, Barr GD, Cowen AE, Ward M, Wood L, Piper DM. Comparison of ranitidine and cimetidine in the treatment of chronic gastric ulcer. A double-blind trial. *Digestion* 1983; **27**: 105–10.

24 Classen M, Dammann HG, Domschke W, *et al.* Abheilungsraten nach Omeprazol- und Ranitidin-Behandlung des Ulcus ventriculi. *Dtsch Med Wochenschr* 1985; **110**: 628–32.

25 Boyd EJS, Wilson JA, Wormsley KG. Smoking impairs therapeutic gastric inhibition. *Lancet* 1983; **i**: 95–7.

26 Bianchi Porro G, Prada A, Lazzaroni M, Petrillo M. Smoking and gastric inhibition by H2 antagonists. [Letter] *Lancet* 1983; **i**: 584.

27 Dammann HG, Walter TA, Müller P. Sekretionshemmung bei Rauchern durch den neuen Imidazol-H2-Rezeptorantagonisten Etintidin. *Dtsch Med Wochenschr* 1985; **110**: 739–40.

28 Deakin M, Ramage JK, Colin-Jones DG, Gray S, Billings J, Williams JG. Does smoking affect the response to cimetidine in duodenal ulcer disease? [Abstract] *Gut* 1985; **26**: A546.

29 Debas HT, Cohen MM, Holubitsky IB, Harrison RC. Effect of cigarette smoking on human gastric secretory response. *Gut* 1971; **12**: 93–6.

30 Whitecross DP, Clarke AD, Piper DW. The effect of cigarette smoking on human gastric secretion. *Scand J Gastroenterol* 1974; **9**: 399–403.

31 Cooper P, Knight JB. Effect of cigarette smoking on gastric secretion of patients with duodenal ulcer. *N Engl J Med* 1956; **255**: 17–21.

32 Schnedorf JG, Ivy AC. The effect of tobacco smoking on the alimentary tract. *JAMA* 1939; **112**: 898–903.

33 Fung WP, Tye CY. Effect of smoking on gastric acid secretion. *Aust N Z J Med* 1973; **3**: 251–4.

34 Murthy SNS, Dinoso VP, Clearfield HR, Chey WY. Simultaneous measurement of basal pancreatic, gastric acid secretion, plasma gastrin, and secretion during smoking. *Gastroenterology* 1977; **73**: 758–61.

35 Steigman F, Dolehide RH, Kaminski L. Effects of smoking tobacco on gastric acidity and motility of hospital controls and patients with peptic ulcer. *Am J Gastroenterol* 1954; **22**: 399–409.

36 Wilkinson AR, Johnston D. Inhibitory effect of cigarette smoking on gastric secretion stimulated by pentagastrin in man. *Lancet* 1971; **ii**: 628–32.

37 Novis BH, Marks IN, Bank S, Sloan AW. The relation between gastric acid secretion and body habitus, blood groups, smoking, and the subsequent development of dyspepsia and duodenal ulcer. *Gut* 1973; **14**: 107–12.

38 Fahrenberg J, Selg H, Hampel R. *Das Freiburger Personlichkeitsinventar FBI*. Gottingen: Hogrefe, 1970.

39 Fimmel CJ, Etienne A, Cilluffo T, *et al*. Long-term ambulatory gastric pH monitoring: validation of a new method and effect of H2-antagonists. *Gastroenterology* 1985; **88**: 1842–51.

40 Randolph EC, Osborne VL, Walkenstein SS, Intoccia AP. High-pressure liquid chromatographic analysis of cimetidine, a histamin H2-receptor antagonist in blood and urine. *J Pharm Sci* 1977; **66**: 1148–50.

41 Carey PF, Martin LE. A high performance liquid chromatography method for the determination of ranitidine in plasma. *J Liquid Chromatogr* 1979; **2**: 1291–303.

42 Gasser Th, Müller HG, Mammitzsch V. Kernels for nonparametric curve estimation. *J R Statist Soc B* 1985; **47**: 238–52.

43 Gasser Th, Müller HG. Estimating regression functions and their derivatives by the kernel method. *Scand J Statist* 1984; **11**: 171–85.

44 Winer BJ. *Statistical principles in experimental design*. New York: McGraw-Hill, 1971.

45 Bortz J. *Lehrbuch der empirischen Forschung*. Berlin: Springer, 1984: 508–18.

46 Bauerfeind P, Cilluffo T, Fimmel CJ, *et al*. Die intragastrale Langzeit-pH-metrie. *Schweiz Med Wochenschr* 1985; **115**: 1630–41.

47 Massarrat S, Enschai F, Pittner PM. Increased gastric secretory capacity in smokers without gastrointestinal lesions. *Gut* 1986; **27**: 433–9.

48 Eyerly JB. Comparative pH values within the stomach, pylorus and duodenum in antacid therapy. *Am J Dig Dis* 1940; **7**: 431–4.

49 Schlotthauer B, Nöller HG. Ergebnisverfälschungen bei der Magenuntersuchung, bedingt durch die Schlauch-technik. *Münchner Med Wochenschr* 1964; **17**: 785–9.

50 Isaac PF, Rand MJ. Cigarette smoking and plasma levels of nicotine. *Nature* 1972; **236**: 308–10.

51 Mahachai V, Walker K, Thomson ABR. Comparison of cimetidine and ranitidine on 24 hour intragastric acidity and serum gastrin profile in patients with esophagitis. *Dig Dis Sci* 1985; **30**: 321–8.

52 Johnson DA, Boyd EJS, Wormsley KG. Altered drug pharmacokinetics in smokers – an effect of smoking on gastric emptying. [Abstract] *Gut* 1985; **26**: A1144–5.

53 Archord JL. Gastric pepsin and acid secretion in patients with acute and healed duodenal ulcer. *Gastroenterology* 1981; **81**: 15–8.

54 Muller-Lissner S. Bile reflux is increased in cigarette smokers. *Gastroenterology* 1986; **90**: 1205–9.

55 Grimes DS, Goddard J. Effect of smoking on gastric emptying. *Br Med J* 1978; **2**: 460–1.

56 Harrison A, Ippoliti A. Effect of smoking on gastric emptying. [Abstract] *Gastroenterology* 1979; **76**: 1152.

57 Ertel G, Herman B, Murthy SNS, Dinoso VP. The effect of smoking on gastroduodenal Motility (GDM), pH changes in the proximal Duodenum (PD), and Gastrointestinal hormones. [Abstract] *Gastroenterology* 1985; **88**: 1375.

58 Brown P. The influence of smoking on pancreatic function in man. *Med J Aust* 1976; **2**: 290–3.

59 Bynum TE, Solomon TE, Johnson LR, Jacobson ED. Inhibition of pancreatic secretion in man by cigarette smoking. *Gut* 1972; **13**: 361–5.

60 Bochenek WJ, Koronczewski R. Effects of cigarette smoking on bicarbonate and volume of duodenal contents. *Am J Dig Dis* 1973; **18**: 729–33.

61 Murthy SNS, Dinoso VP, Clearfield HR, Chey WY. Serial pH changes in the duodenal bulb during smoking. *Gastroenterology* 1975; **75**: 1–4.

62 McCloy RF, Greenberg GR, Baron JH. Duodenal pH in health and duodenal ulcer disease: effect of meal, Coca-Cola, smoking and cimetidine. *Gut* 1984; **25**: 386–92.

63 Nagata M, Okuma Y, Osumi Y. Effects of intracerebroventricularly applied nicotine on enhanced gastric acid secretion and mucosal blood flow in rats. *Eur J Pharm* 1984; **101**: 185–91.

64 Naitove A, Constantian MB, Arkins T. Gastric hemodynamik effects of smoking and nicotine. [Abstract] *Gastroenterology* 1970; **58**: 1058.

65 Sonnenberg A, Husmert N. Effect of nicotine on gastric mucosal blood flow and acid secretion. *Gut* 1982; **23**: 532–5.

66 Fung WP, Mahoney DP, Beilin LJ. Effect of cigarette smoking on gastric secretion of 6-keto prostaglandin F1a. *Aust N Z J Med* 1982; **12**: 206–10.

67 Quimby GF, Avunduk Bonnice C, Burstein SH, Eastwood GL. Active smoking depresses prostaglandin synthesis in human gastroduodenal mucosa. [Abstract] *Gastroenterology* 1985; **88**: 1548.

68 Jusko WJ. Role of tobacco smoking in pharmacokinetics. *J Pharm Biopharm* 1978; **6**: 7–39.