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Does smoking influence the pharmacokinetics and pharmacodynamics of the H_2-receptor antagonist famotidine?

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Twelve healthy habitual cigarette smokers and eight non-smokers participated in a double-blind placebo controlled study to determine the effect of smoking on the pharmacokinetics and pharmacodynamics of the H_2-receptor antagonist famotidine. In smokers, cigarette smoking was standardised and started 1 h before (A), or 2 h after (B) drug administration, or was prohibited (C). Intragastric pH-levels (IGpH) were measured with an ambulatory pH-recorder. Famotidine (40 mg orally) significantly raised median 22 h IGpH in non-smokers and smokers in all study periods. The smoking sequence (A, B, C) did not significantly influence median 22 h IGpH in both placebo-treated and famotidine-treated smokers, and no significant difference in median 22 h IGpH was shown between smokers and non-smokers. Plasma drug concentrations were similar in the various experiments, although famotidine was detected earlier in plasma from non-smokers compared with smokers ($P < 0.05$). Smoking did not interfere significantly with the pharmacokinetics and pharmacodynamics of famotidine.

Keywords famotidine histamine H_2-receptor antagonist smoking pharmacokinetics pharmacodynamics

Introduction

Peptic ulcer patients who smoke are reported to have lower healing rates and higher relapse rates when treated with histamine H_2-receptor antagonists than non-smokers (Korman *et al.*, 1983). This impaired therapeutic response to H_2-receptor antagonists may be due to decreased inhibition of gastric acid secretion (Bauerfeind *et al.*, 1987; Boyd *et al.* 1983; Schürer-Maly *et al.*, 1989) or to alteration in pharmacokinetics in smokers (Boyd *et al.*, 1987) using antisecretory drugs. Pharmacokinetic and pharmacodynamic studies with H_2-receptor blockers in smokers have not been performed simultaneously in the same individuals. Furthermore, no data are available on the effect of smoking on the sensitivity to H_2-receptor blockers in smokers. This may be relevant as it has been shown that both pharmacokinetic and pharmacodynamic factors contribute to variability in the antisecretory effect of famotidine (Echizen *et al.*, 1988).

Therefore, we have studied both the effect of smoking and abstinence from smoking on the pharmacokinetics and pharmacodynamics of famotidine in habitual smokers. Non-smokers were included as matched controls.

Methods

This double-blind, placebo-controlled randomised cross-over study was carried out in 12 healthy habitual smokers (seven women, five men, mean age 24 years, range 21–25) and eight non-smokers (four women, four men, mean age 24 years, range 20–30). A habitual smoker was defined as a person who smoked 10 cigarettes or more a day for at least 3 years. Pre-entry physical examination, laboratory tests and ECG revealed no abnormalities. The study was approved by the local ethics committee of the University Hospital Leiden. Each subject gave written informed consent.

On separate days each volunteer received either placebo or famotidine (40 mg by mouth), to be ingested 15 min after a standard breakfast at 10.00 h. Non-smokers did not smoke during the various experiments, while smokers smoked one cigarette (Camel®) every 30 min, starting 1 h before (A), or 2 h (B) after drug administration, up to a total of 20 cigarettes. In study period C the smokers were not allowed to smoke. Blood samples for the measurement of plasma famotidine were taken before drug dosage and every 30 min afterwards for 8 h. Urine was collected over 24 h. The

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subjects were fully ambulatory and food and fluid intake were standardized. A combined glass electrode (model '440 m4', W. Ingold AG, Urdorf, Switzerland), connected with a solid state device (Proxima Light, Mantova, Italy), was positioned in the stomach at 08.30 h for ambulant measurement of intragastric pH as decided by Baak *et al.* (1991). This was removed at 08.00 h the next morning.

Famotidine concentration in plasma and urine were measured by reversed-phase h.p.l.c. assay with u.v.-detection (De Lepeleire *et al.*, 1990). The limit of determination was 5 ng ml^{-1} plasma and 0.1 $\mu g\ ml^{-1}$ urine.

C_{max} and t_{max} values were noted directly from the data; $t_{½z}$ was calculated by log-linear regression of the terminal data points; AUC(0,8 h) was calculated using the linear trapezoidal rule and AUC(0,∞) by extrapolation using $C(last)/\lambda_z$. The lag time (t_{lag}) was defined as the mid-point in time between the last sample with undetectable and the first sample with a measurable concentration of famotidine. Latency was defined as the time between administration of famotidine and the onset of the effect of intragastric pH, i.e. a pH greater than 4.0 for at least 10 min.

Statistical analyses were performed by non-parametric one- and two-way analysis of variance (ANOVA), linear regression and analysis of co-variance (ANCOVA).

Results

There was a small but significant difference ($P < 0.05$) in t_{lag} for plasma famotidine concentration between non-smokers and smokers (Table 1). Other pharmacokinetic parameters were similar in non-smokers and smokers, irrespective of smoking sequence (Table 1).

Famotidine (40 mg) raised median 22 h intragastric pH in non-smokers (Figure 1b) and in smokers (Figure 1d) in all study periods compared with placebo (medians; interquartile ranges); non-smokers: 1.50 (1.15–1.80) to 3.25 (2.55–3.90), $P < 0.01$; smokers A: 1.35 (1.12–1.75) to 2.55 (2.12–4.22), B: 1.55 (1.18–1.88) to 2.45 (2.25–3.65), C: 1.40 (1.10–1.60) to 2.45 (2.05–3.22), placebo and famotidine 40 mg, respectively, $P < 0.005$). During the placebo experiments there was no significant difference in intragastric pH in non-smokers compared with smokers (Figure 1a), irrespective of smoking sequence (Figure 3a).

The onset of the effect of famotidine (latency) correlated significantly with both t_{lag} ($r = 0.98$; $P < 0.005$) and t_{max} ($r = 0.85$; $P < 0.002$). A significant correlation was found between AUC(0,8) and the median pH during the same 8 h period ($r = 0.82$, $P < 0.0001$). Analysis of co-variance did not demonstrate significant differences in pH values between smokers and non-smokers when differences in the AUC of famotidine were taken into account. There was no significant interaction of smoking in relation to treatment ($F = 0.147$, $P > 0.9$).

Discussion

The results indicated no major differences in the pharmacokinetic parameters of famotidine in smokers and non-smokers, although oral drug absorption was significantly delayed in smokers. Absorption was unaffected by abstinence from smoking during drug administration (period B and C). Since famotidine was administered immediately after a standard breakfast a delayed gastric emptying of solids reported in smokers (Miller *et al.*, 1989; Nowak *et al.*, 1987) may account for the delayed absorption. However, the literature on gastric emptying in smokers is contradictory (Grimes & Goddard, 1978; Miller *et al.*, 1989; Nowak *et al.*, 1987). The delayed absorption was not accompanied by a change in AUC (< 10%) nor in a marked delay in onset of antisecretory effect. Changes in AUC up to 15% have not been considered to be clinically relevant (Lin *et al.*, 1987). In our study 20% differences in AUC values between non-smokers and smokers, and 15% differences in relation to the smoking regimen would have been detected with $\alpha = 0.05$ and 1-β of 0.85–0.95.

During placebo treatment there was no difference in median 22 h intragastric pH between non-smokers and smokers irrespective of their smoking behaviour during

Table 1 Pharmacokinetic parameters deciding the fate of famotidine (40 mg p.o) in non-smokers ($n = 8$) and smokers when smoking (A), smoking starting 2 h post dose (B), and when not smoking (C) ($n = 12$). Values are given as mean and 95% confidence interval

		C_{max} ($ng\ ml^{-1}$)	t_{lag} (h)	t_{max} (h)	$t_{½,z}$ (h)	AUC(0,8) ($ng\ ml^{-1}\ h$)	AUC ($ng\ ml^{-1}\ h$)	Ae (% dose occured unchanged)
Non-smokers		124 (99–149)	0.6 (0.3–0.9)	2.8 (2.0–3.6)	2.5 (1.9–3.0)	560 (436–683)	727 (570–884)	39 (32–45)
Smokers	A	119 (95–142)	1.1* (0.8–1.4)	3.5 (3.0–4.0)	2.8 (2.4–3.2)	562 (459–666)	815 (663–968)	39 (33–44)
	B	124 (103–145)	0.9* (0.6–1.1)	3.3 (2.7–3.9)	2.8 (2.2–3.4)	565 (473–657)	774 (658–889)	37 (33–41)
	C	121 (98–144)	1.0* (0.9–1.2)	3.5 (2.7–4.3)	3.1 (2.3–3.8)	546 (427–666)	786 (608–964)	37 (30–43)

*$P < 0.05$, compared with non-smokers.

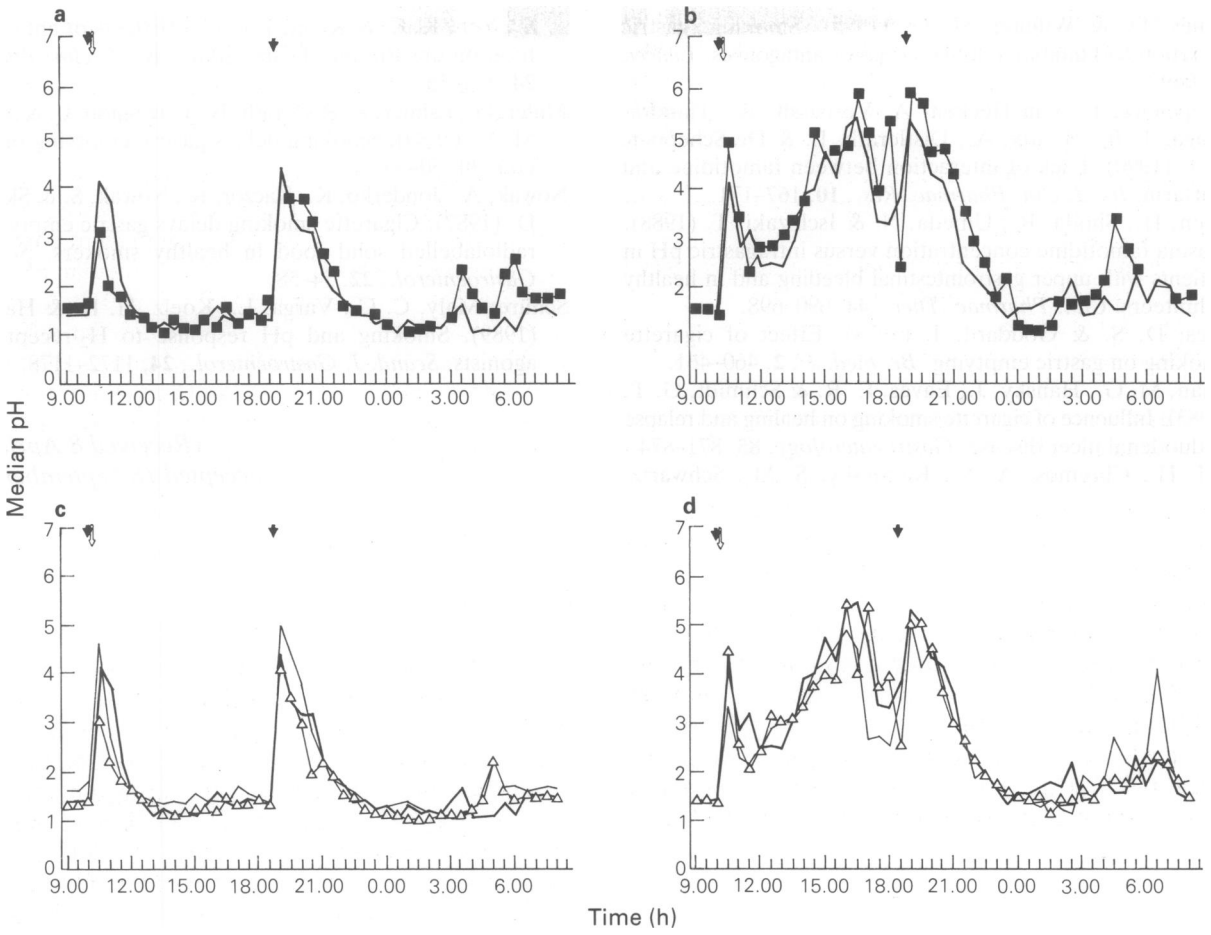

Figure 1 Median intragastric pH over 24 h after administration of placebo (a,c) or famotidine 40 mg (b,d). Non-smokers: closed squares (a,b) (n = 8). Smokers: smoking from 09.00 h (thick line a,b,c,d); smoking from 12.00 h (thin line c.d); not smoking (triangles, c,d) (n = 12). Meals are indicated by filled arrows and drug administration by open arrows.

the study period. It is likely that smoking has no consistent, clinically important effect on gastric acid secretion (Bauerfeind *et al.*, 1987).

Smoking did not influence the effect of famotidine on intragastric pH. This was consistent with the results of some (Bianchi-Porro *et al.*, 1983; Deakin *et al.*, 1985) but not all (Bauerfeind *et al.*, 1987; Boyd *et al.*, 1983; Schürer-Maly *et al.*, 1989) studies with other H_2-receptor antagonists. However, in all previous studies plasma drug concentrations were not measured. We have shown that individual responses to famotidine correlated significantly with famotidine AUC and that the kinetics of the drug were similar in smokers and non-smokers. When pH-values were analysed with famotidine AUC as a covariable (ANCOVA) no difference was demonstrated between non-smokers and smokers, irrespective of smoking behaviour. Therefore, our data suggest that the sensitivity of smokers to famotidine is comparable to that of non-smokers and that inter-individual variability in response to famotidine is similar in smokers and non-smokers. Although healthy volunteers were examined rather than ulcer patients, it has been suggested that patients respond to smoking in a similar way (Bauerfeind *et al.*, 1987).

In conclusion, our data suggest that smoking does not influence either the pharmacokinetics or the pharmacodynamics of the H_2-receptor antagonist famotidine. They do not support the hypothesis that the pharmacological response to H_2-receptor antagonists is impaired in smokers.

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