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Nil effect of cigarette smoking on ranitidine pharmacokinetics

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Summary

Ranitidine (150 mg) was administered to smoking and non-smoking healthy male volunteers. Statistical analysis on the calculated pharmacokinetics parameters showed that the differences were insignificant.

Ranitidine is a potent H-2 receptor antagonist which is commonly used for the treatment of peptic ulcers. Ranitidine pharmacokinetics vary with age (Greene et al., 1986), and pathological state (Ilett et al., 1986; Gonzales-Martin et al., 1987).

Smoking is recognised as a factor in the development and recurrence of peptic ulcers (Bianchi Porro and Parente, 1991), thus cigarette smokers are expected to constitute an important group of peptic ulcer patients to whom ranitidine is administered. It has been reported that cigarette smoking affects drug metabolism and disposition (Jusko, 1978; Vahakangas et al., 1983). The present report investigates the effect of cigarette smoking on ranitidine pharmacokinetics in healthy male volunteers.

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Seven subjects were non-smokers (mean age 25 ± 4.1 years; mean body weight 74.8 ± 11.2 kg) and seven were regular smokers who had been smoking a minimum of 20 cigarettes a day for the past 3 years (mean age 27.4 ± 4.5 years; mean body weight 66.4 ± 10 kg). All subjects signed a constant form and the protocol was approved by the Ethical Committee on Human Research.

A single dose of purchased ranitidine tablets containing 150 mg of ranitidine HCl was administered. Venous blood samples were drawn at specified intervals over 8 h. The samples were analysed for ranitidine constants using a reported chromatographic method (Sheikh Salem et al., 1988).

The pharmacokinetic parameters were calculated from the plasma concentration-time profile for each subject using the RSTRIP computer program (Rstrip, Exponential curve stripping and parameter estimation, MicroMath Scientific Software, Salt Lake City, UT, U.S.A.), based on a one-compartmental model.

TABLE 1

Summary of individual pharmacokinetics parameters following the administration of one tablet (150 mg ranitidine) to non-smokers

Subject	$T_{1/2e}$ (h)	$T_{1/2a}$ (h)	T_{max} (h)	C_{max} (μg ml^{-1})	AUC_t (μ h ml^{-1})	AUC_∞	K_e (h^{-1})	K_a
H.B.	1.26	0.87	1.54	0.57	2.32	2.41	0.54	0.79
N.M.	1.62	1.00	1.92	0.53	2.50	2.73	0.42	0.69
M.A.	1.56	0.85	1.69	0.55	2.43	2.60	0.44	0.8
R.M.	2.60	0.72	1.86	0.54	2.77	3.32	0.26	0.95
N.G.	1.48	0.98	1.79	0.72	3.27	3.50	0.46	0.70
S.M.	1.48	0.78	1.56	0.64	2.68	2.83	0.46	0.88
A.M.	1.47	0.97	1.75	0.43	1.95	2.08	0.46	0.71
Mean	1.63	0.88	1.73	0.56	2.56	2.63	0.43	0.78
±S.D.	0.43	0.10	0.14	0.09	0.40	0.45	0.08	0.09

The calculated pharmacokinetic parameters for each volunteer were: area under the curve AUC_∞ (0–∞), AUC_t (0–8 h), elimination half-life $T_{1/2e}$, absorption half-life $T_{1/2a}$, T_{max}, C_{max}, elimination rate constant K_e and absorption rate constant K_a.

Statistical analysis was performed using Student's *t*-test. The pharmacokinetic parameters, and their mean and standard deviation values were calculated and are listed in Tables 1 and 2 for non-smokers and smokers, respectively. Inter-subject variations were greater among smokers, which might reflect variation in the social habits of the tested group. However, the mean values for both groups were in close agreement with similar data reported for raniditine (Garg et al., 1983; Leeder et al., 1984). Upon statistical comparison between the two sets of data, it was found that the differences were statistically insignificant at $P < 0.05$.

To gain further insight, means of plasma concentrations at each time point were determined and a plot was constructed for each group. Fig. 1 shows the observed and the computer fitted data for the smokers and non-smokers. The plot indicates a difference in C_{max}, however, analysis by *t*-test confirmed the insignificance of the observed variation. The elimination phases of ranitidine in smokers and non-smokers were close to each other, as indicated by the plot in Fig. 1 and the data of Tables 1 and 2. This would suggest that cigarette smoking does not interfere with ranitidine metabolism and elimination. Cigarette smoking is assumed to affect drug metabolism

TABLE 2

Summary of individual pharmacokinetics parameters following the administration of one tablet (150 mg ranitidine) to cigarette smokers

Subject	$T_{1/2e}$ (h)	$T_{1/2a}$ (h)	T_{max} (h)	C_{max} (μg ml^{-1})	AUC_t (μg h ml^{-1})	AUC_∞	K_e (h^{-1})	K_a
H.M.	2.28	1.60	2.89	0.38	2.25	2.92	0.30	0.43
F.N.	1.91	1.14	2.21	0.48	2.50	2.87	0.36	0.60
M.K.	2.48	1.28	2.60	0.36	2.11	2.68	0.27	0.53
M.M.	3.29	0.37	1.33	0.56	2.79	3.53	0.21	1.86
G.M.	1.47	0.96	1.77	0.66	2.95	3.15	0.46	0.71
M.S.	2.16	0.79	1.84	0.41	2.05	2.34	0.32	0.86
S.A.	1.56	0.56	1.30	0.63	2.42	2.53	0.44	1.23
Mean	2.16	0.95	1.99	0.49	2.43	2.86	0.33	0.88
±S.D.	0.61	0.42	0.60	0.12	0.33	0.39	0.08	0.50

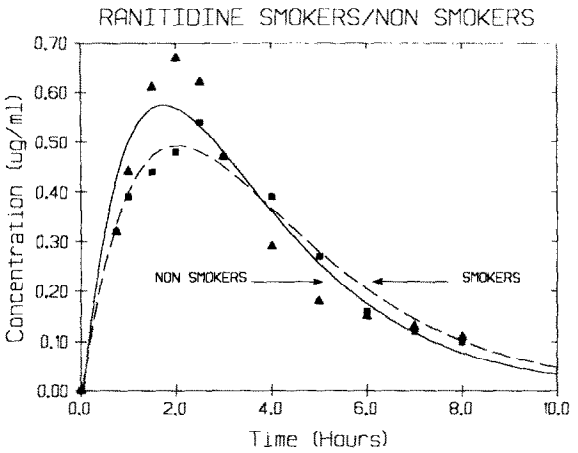

Fig. 1. Mean plasma concentrations of ranitidine in non-smokers (▲) and smokers (■) plotted vs time and fitted to the one-compartment model.

through induction of cytochrome P-450 (Jusko, 1978). Earlier reports indicated that ranitidine, unlike cimetidine, is not a substrate for cytochrome P-450 (Randic et al., 1983) although N and S oxidation products are among the most important metabolites of ranitidine (Garg et al., 1983).

In conclusion, the present work has demonstrated that cigarette smoking does not effect the pharmacokinetic parameters of ranitidine significantly.

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