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NO SIGNIFICANT EFFECT OF CIMETIDINE ON THE PHARMACOKINETICS OF MISONIDAZOLE IN MAN

Misonidazole, a 2-nitroimidazole, is under clinical trial as an agent that potentiates the effects of ionising radiation on hypoxic tumour cells. At high doses, use of the drug is limited by neurological toxicity which may result in peripheral neuropathy and occasionally convulsions (Dische *et al.*, 1979).

Studies in this laboratory and elsewhere have shown that the rate of metabolism of misonidazole can be influenced by other drugs such as phenytoin and phenobarbitone (Williams *et al.*, 1983; Workman *et al.*, 1980). Induction of metabolism may reduce the neurotoxicity of misonidazole by decreasing tissue exposure to the drug. Similarly, drugs which inhibit the metabolism of misonidazole may lead to increased toxicity.

The clinical circumstances in which misonidazole is used make it likely that cimetidine will often be administered concurrently. Recent reports in the literature have highlighted increasing instances of drug interactions involving cimetidine based on its inhibitory effects upon cytochrome P-450-mediated oxidative metabolism (Somogyi & Gugler, 1982).

The major known metabolic pathway of misonidazole involves demethylation to desmethylmisonidazole (Flockhart *et al.*, 1978) suggesting that misonidazole could be subject to the enzyme-inhibiting effect of cimetidine.

The present study was designed to determine if there was a significant pharmacokinetic interaction between cimetidine and misonidazole in healthy volunteers.

Six normal volunteers, four males and two females, age ranging from 21 to 30 years and weights 55 to 73 kg, participated in the study. Misonidazole elimination kinetics were studied before and after a 1 week course of cimetidine. All subjects initially received a dose of misonidazole (1.0 g/m²) taken orally with water (200 ml). Blood samples (10 ml) were collected at increasing intervals over 48 h (15 samples).

After a period of at least 1 week following the misonidazole dose, cimetidine 200 mg three times daily with meals and 400 mg at night was taken for 9 days. The order was not randomized because the time-course of 'washout' of enzyme inhibition has not been established. The clearance (CL), the half-life ($t_{1/2}$) and the volume of distribution (V_d) were calculated using the following relationships:

$$t_{1/2} = 0.693/\beta$$

$$CL = F \times \text{Dose}/AUC$$

$$V_d = CL/\beta$$

where β is the slope of the terminal phase of the exponential plasma concentration/time curve and F the fraction of the dose absorbed. The AUC up to the last point was calculated using the trapezoidal rule and then extrapolated to infinite time by dividing the final concentration by β . The CL and V_d were calculated assuming 100% oral availability ($F = 1.0$) (oral availability 85-100%, Schwartz, personal communication). The time to peak (t_{max}) and the peak concentration ($C_{p_{max}}$) were also noted. Statistical

Table 1 Pharmacokinetic parameters for misonidazole before and after cimetidine treatment

Subject	$t_{1/2}$ (h)		V_d (l)		CL (ml min ⁻¹)		AUC ($\mu\text{g ml}^{-1}$ h)		AUC _{0-48 h} O-desmethylmisonidazole ($\mu\text{g ml}^{-1}$ h)	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	10.2	9.2	32.5	33.4	37.0	41.8	676	598	80.1	59.3
2	9.5	9.2	30.1	33.0	36.4	41.6	732	642	110.1	111.4
3	10.2	11.2	35.4	34.0	40.1	35.0	748	857	97.8	95.5
4	11.1	11.2	46.0	45.1	47.8	46.6	662	680	76.5	79.9
5	10.9	11.5	33.6	34.2	35.6	34.3	843	875	94.6	86.3
6	13.6	13.0	36.4	32.4	31.0	28.8	861	926	88.3	65.5
Mean	10.9	10.9	35.7	35.4	38.0	38.0	754	763	91.2	83.0
s.d.	1.4	1.5	5.5	4.8	5.6	6.5	83	139	12.3	19.2
P value	0.7		0.57		0.76		0.59		0.09	

analyses were performed using the paired *t*-test. The values are given as the mean $\pm$ s.d.

There were no significant differences in the mean data for AUC, $t_{1/2}$, CL, V_d , t_{max} or Cp_{max} for misonidazole after cimetidine treatment nor for the mean AUC for desmethylmisonidazole (Table 1). The mean Cp_{max} was 42.1 ± 4.4 μ g/ml before and 43.0 ± 3.8 μ g/ml after ($P = 0.40$) and the t_{max} 1.99 ± 1.42 h before and 1.69 ± 1.17 h after ($P = 0.53$) cimetidine.

Various types of oxidative reactions are inhibited by cimetidine, including hydroxylation, *N*-desmethylation and *O*-deethylation (Pelkonen & Puurunen, 1980). Why cimetidine should inhibit desmethylation of some drugs and not others is not clear but may be explained by multiple forms of P-450. A failure to inhibit glucuronidation (phase II reaction) has been reported (Patwardhan *et al.*, 1980) but not of phase I oxidative reactions. Less than 3% of a given dose of misonidazole is eliminated in the urine in 48 h as glucuronide conjugates (Holbrooke, personal communication).

It is possible that a higher dose of cimetidine, or a longer duration of administration, could inhibit the metabolism of misonidazole. Patients, particularly if elderly with impaired renal function, would likely

have higher blood cimetidine concentrations than normal volunteers. However, doses of less than 100 mg/day and given for less than 1 week have been sufficient to demonstrate inhibition of the metabolism of other drugs, (Somogyi & Gugler, 1982).

Although no alternation in misonidazole dose appears necessary if cimetidine is administered concurrently, routine monitoring of misonidazole is recommended, as misonidazole has a low therapeutic index.

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THE EFFECT OF INDORAMIN INFUSION ON APPARENT LIVER BLOOD FLOW IN MAN

In man, alterations in liver blood flow have important pharmacokinetic implications. Cimetidine therapy reduces apparent liver blood flow, and thus reduces the clearance of intravenous and oral propranolol (Feely *et al.*, 1981) and intravenous lignocaine (Feely *et al.*, 1982). Animal work has demonstrated vasoconstrictor α -adrenoceptors in the hepatic artery and portal vein (Richardson & Withington, 1981) and we postulated that blocking these receptors would increase apparent liver blood flow. We have studied the effect of indoramin (an α -adrenoceptor blocking drug) recently introduced for the management of hypertension, on apparent liver blood flow in man

using the clearance of indocyanine green as described by Caesar *et al.* (1961) and Feely *et al.* (1981).

Three male and three female healthy volunteers aged 20 to 25 years participated in the study. No medication was taken during the week prior to the study which was double-blind and crossover. Written informed consent was obtained. The volunteers arrived in the department after an overnight fast, and rested supine for 20 min. Two butterfly cannulae were inserted, one in each forearm. One cannula was used for the drug or placebo infusion and venous sampling, and the other was used for injection of indocyanine dye (ICG). Indoramin 20 mg (2 mg/ml)