PLASMA CONCENTRATION-RESPONSE RELATIONSHIP FOR CIMETIDINE INHIBITION OF DRUG METABOLISM IN THE RAT

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Although widely used in the treatment of peptic ulcers, cimetidine has been demonstrated to inhibit the metabolism of a number of drugs which are oxidised via the hepatic cytochrome P-450 system (Bauman and Kimelblatt, 1982). Cimetidine is unique among the other well established inhibitors in that within the therapeutic range it exerts mild yet clearly demonstrable inhibitory effects and therefore ethical constraints do not limit cimetidine-drug interaction studies to animal models. Data would indicate that these interactions are dose dependent, however no information is available on the relationship (if any) between plasma concentration of cimetidine and inhibitory response. We have investigated the relationship between various steady-state plasma concentrations of cimetidine and the inhibition of drug metabolism using antipyrineas a marker of hepatic cytochrome P-450 activity in the rat (Rhodes et al 1984).

Cimetidine and antipyrine were analysed simultaneously by HPLC using a 25cm Spherisorb 5µm silica column, a mobile phase consisting of 5% water in acetonitrile with 0.2% ammonia and UV detection at 228nm. Sample preparation consisted of the addition of methylene chloride to a basified plasma sample (100µl) to which internal standard had been added (SKF 92374, 15µg/ml), mixing and centrifugation to separate the phases. The organic phase was evaporated to dryness and then reconstituted in 100µl of eluent prior to injection. The method showed linearity up to a concentration of 50µg/ml, a 3.5% coefficient of variation at 10µg/ml and a minimum detection limit of 0.5µg/ml. The sulphoxide metabolite of cimetidine was well resolved from the parent compound and antipyrine.

Male Sprague-Dawley rats, implanted with cannulae in the jugular vein and carotid artery the day before the study, were administered cimetidine i.p. (2 - 80mg/kg) supplemented with an infusion of cimetidine (1 - 20mg/h) into the jugular cannula to maintain a required steady-state concentration. Control rats were given equivalent volumes of saline, the vehicle used for cimetidine. Antipyrine (50mg/kg) was given as a bolus injection and serial samples removed over 8h. Marked inhibition of hepatic cytochrome P-450 activity is evident in both antipyrine clearance and half-life at all cimetidine concentrations (see Table 1). In contrast antipyrine volume of distribution remained constant. The degree of inhibition is related to the cimetidine concentration in a non-linear fashion. Approximately 50% inhibition occurs at a plasma cimetidine concentration of 1.25mg/L. Detailed analysis of the relationship between cimetidine concentration and hepatic cytochrome P-450 activity (via antipyrine clearance) indicate two classes of binding sites - a low affinity, high capacity site and a high affinity, low capacity site.

Table 1 - Antipyrine disposition parameters at different cimetidine steady-state concentrations.

Study	Cimetidine steady state conc (mg/L)	Clearance (ml/h/kg)	Half-life (min)	Volume of distribution (L/kg)
1 (n = 13)	0	519 ± 186	95 ± 34	1.1 ± 0.2
2 (n = 8)	1.25 ± 0.17	290 ± 48*	248 ± 42*	1.2 ± 0.2
3 (n = 11)	3.52 ± 0.78	103 ± 19*	395 ± 109*	0.9 ± 0.1
4 (n = 10)	16.48 ± 2.22	51 ± 15*	849 ± 184*	1.0 ± 0.1
5 (n = 7)	45.23 ± 4.44	39 ± 7*	937 ± 181*	0.9 ± 0.1

Mean ± s.d. *Statistical difference from control

Bauman, J.H., Kimelblatt, B.J., Drug Intell. Clin. Pharm. 16: 380-386, 1982.
Rhodes, J.C., Hall, S.T., Houston, J.B. Xenobiotica 14: 677-686, 1984.