IN-VIVO DETERMINATIONS OF THE POTENCY OF KETOCONAZOLE IN INHIBITING DRUG METABOLISM IN THE RAT

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The inhibitory effects of a variety of imidazole derivatives on drug metabolism *in-vitro* and *in-vivo* is well documented (Testa & Jenner 1981). Ketoconazole, an imidazole antimycotic agent, has been shown to inhibit the hepatic oxidative metabolism of certain drugs in animals (Meredith *et al.* 1985). Ketoconazole is thought to act on mycotic infections by inhibiting the fungal cytochrome P-450 mediated 14α-demethylation step in ergosterol biosynthesis, which is an important component in fungal cell membranes. Ketoconazole has non-linear pharmacokinetics hence, we decided to investigate the dose-dependency of the inhibition by ketoconazole of antipyrine pharmacokinetics, a marker of drug-metabolising capacity (Rhodes & Houston 1983) and to obtain an *in-vivo* estimate of K_I (Inhibitor dose giving 50% reduction in antipyrine elimination rate).

Male Sprague-Dawley rats (n=27) were divided into nine groups of three. Each group received one of nine different doses of ketoconazole (0, 1, 3, 5, 10, 15, 20, 30 or 50 mg/kg in 10% cremophor, 90% 0.1N HCl, 10ml/kg ; i.p.). One hour later each rat was injected with N-methyl-^{14}C-antipyrine (25mg/kg, 10μCi/kg; i.p.). The rats were housed in all glass metabolism cages to allow continuous collection of $^{14}CO_2$ (derived from N-demethylation) and urine. $^{14}CO_2$ exhalation rate (CER) time profiles were plotted for each rat and various antipyrine kinetic parameters determined. The results are shown graphically. Inhibition was pronounced and dose-related. The CER_{MAX} decreased and broadened with increasing dose. At lower doses (1-20mg/kg) a terminal phase was observed due to ketoconazole elimination during the study. At higher doses, ketoconazole levels were sufficiently high as to maintain a plateau for the duration of the experiment (10h.). An *in-vivo* K_I was obtained graphically using a plot of I/CER_{MAX} *versus* inhibitor dose (11.9mg/kg) and by non-linear regression analysis of the CER data (5.2mg/kg). The slight discrepancy between the two values can be explained by the fact that the non-linear equation allowed for elimination of the inhibitor during the study. These data demonstrate that the inhibitory response to ketoconazole is dependent on both its K_I and its pharmacokinetics.

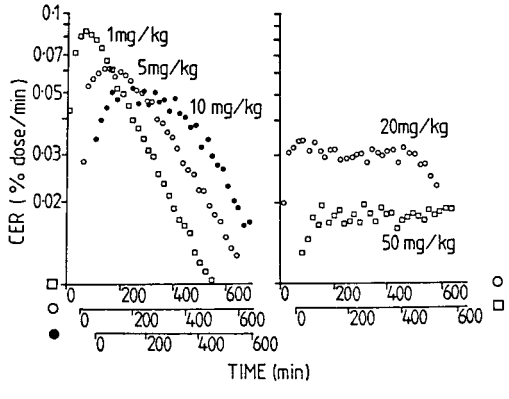

FIGURE. Antipyrine CER-time profiles for various ketoconazole doses.

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