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Interindividual variation in apparent volumes of distribution of antipyrine in the rat

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Antipyrine pharmacokinetics have frequently been employed as a measure of in vivo rate of hepatic drug metabolism both in man and animals (Vesell & Page 1968; Bakke et al 1974; Stevenson 1977; Aarbakke 1978; Vesell 1979; Gadeholt et al 1980; Høyem-Johansen et al 1980). In these studies various kinetic variables have been used as indices of the hepatic metabolic capacity. Recently a thorough discussion of the relationship between antipyrine clearance, half-life and apparent volume of distribution in man was presented (Sultatos et al 1980). Analysis of pooled data from several studies of antipyrine in man revealed that over the range of commonly observed clearance values in healthy volunteers, the relationship between antipyrine clearance and half-life approximated linearity. It was further stated that changes in β or $t_{1/2}(\beta)$ reflect altered antipyrine elimination, provided that the apparent volume of distribution (V_β) is unchanged. The latter statement must, however, be qualified, because unchanged V_β is a prerequisite for the use of β or $t_{1/2}(\beta)$ both in experiments designed for interindividual and intraindividual comparison. In man, insignificant variation of the apparent volume of distribution of antipyrine has been reported in both types of studies (Roberts et al 1976; Sultatos et al 1980).

Recently, significant intraindividual variation of both V_c and V_β upon repeated testing of antipyrine kinetics in cannulated, but otherwise untreated rats, were demonstrated (Johannessen et al 1981). Thus, the validity of β and $t_{1/2}(\beta)$ as single measures of changes in antipyrine elimination in studies using rats as their own controls might be questioned. In this communication we present data on the interindividual variation of antipyrine apparent volumes of distribution, V_c, V_β and $V_{d(ss)}$, in a population of cannulated, but otherwise untreated rats.

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Materials and methods

Eighteen Male Wistar rats, 200–300 g, were studied. In fluanison/fentanyl anaesthesia (0·6/0·13 mg kg^{-1}), an inguinal artery and vein were cannulated with PE 50 tubing previously filled with heparinized 0·9% NaCl, the indwelling part of the tubing having been stretched to reduce its diameter and lubricated with silicone oil to facilitate insertion. The cannula was secured and the tubing was transferred dorsally through a subcutaneous tunnel and made accessible through a skin perforation in the lumbar region. After the surgery, 3 ml sterile 0·9% NaCl (saline) was injected s.c. in the rat to compensate for fluid losses. The rats were placed in restraining cages overnight and allowed free access to food and water. Pharmacokinetic experiments were conducted the next morning, 12–15 h after the cannulation. Antipyrine-*N*-methyl[^{14}C] (New England Nuclear) 15 mg kg^{-1}, 1–2 μCi/animal, was infused via the cannula in the inguinal vein and dissolved in a volume of 0·6–0·9 ml saline. The infusion, lasting for 30 s, was immediately followed by flushing of the cannula with 0·5 ml saline. Blood samples (0·1 ml) were drawn from the cannula in the inguinal artery 3, 6, 9, 15, 20, 30, 40, 60, 90, 120, 150 and 180 mm after dosing.

Concentrations of antipyrine in whole blood was determined essentially by the extraction method of Bakke et al (1974).

The data were analysed according to a two-compartment

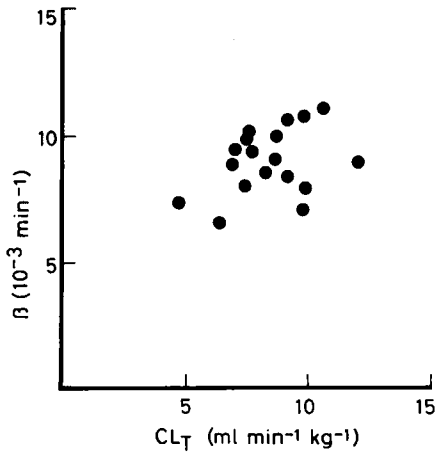

FIG. 1. Relationship between observed values for β and Cl_T of antipyrine in 18 rats. Correlation analysis of β versus Cl_T demonstrated no statistically significant correlation between β and Cl_T; $\beta = 6{\cdot}72 \pm 0{\cdot}27\ Cl_T$, r = 0·35.

open model with first order elimination kinetics. Total clearance was calculated by dose/(A/α + B/β) where A and B are γ-intercepts of the extrapolated lines of the α- and β-phase, respectively. V_c was calculated by Dose/A + B. V_β was obtained by dividing total clearance by β. $V_{d(ss)}$ was calculated by the equation:

$$V_{d(ss)} = V_1 \left[\frac{k_{12} + k_{21}}{k_{21}}\right], \text{where } V_1 = \frac{\text{dose}}{C_o}$$

Results

In Table 1 the values for the various apparent volumes of distribution are listed. The relationship between observed total clearance and β is shown in Fig. 1. Linear correlation analysis showed that there was no significant correlation between the observed values for CL_T and β.

Discussion

The results demonstrate a considerable variation among individual rats in all apparent volumes of distribution. The elimination dependent variable, V_c and V_β, varied most, by a factor of 1·8 and 2·0, respectively, while the elimination independent variable $V_{d(ss)}$ varied by a factor of 1·6.

The relationship between total clearance and β is given by the equation $\beta = CL_T/V_\beta$, and accordingly a plot of β as a function of CL_T would give a straight line if there was no variation in the Vβ between individual rats. As demonstrated in Fig. 1, this is not so. Furthermore, the *r* value of 0·35 in our weight-corrected population is considerably lower than the *r* values of 0·68 and 0·55 reported in two human populations without weight-correction (Sultatos et al 1980).

The variation of antipyrine apparent volumes of distribution demonstrated in this study has two important implications: firstly, the presented variation in the elimination dependent apparent volumes of distribution must be considered, when differences in elimination data between groups of rats are interpreted in terms of metabolic capacity of the liver. Secondly, the values reported here for the elimination independent variable ($V_{d(ss)}$), which should be used for comparison of volume of distribution between different individuals (Klotz 1976), demonstrates that antipyrine distribution in this species is not uniform but subject to considerable individual variation. Furthermore, this variation is of the same order of magnitude as the variation in rate of hepatic drug metabolism, expressed as CL_T (Fig. 1).

Table 1. Apparent volumes of distribution, V_β, V_c and $V_{d(ss)}$ in 18 rats. The values were calculated from antipyrine concentration data in whole blood taken from a catheter in an inguinal artery.

Kinetic variable	Range	Mean	Standard deviation
V_β (litre kg^{-1})	0·73–1·46	1·0	0·21
V_c (litre kg^{-1})	0·47–0·87	0·63	0·13
$V_{d(ss)}$ (litre kg^{-1})	0·82–1·30	0·96	0·16

Since the volume of distribution is a useful pharmacokinetic variable relating drug concentrations in plasma to the total amount of drug in the body, a change in apparent volume of distribution induced by various factors may well result in a change in therapeutic or toxic significance of a given plasma level. Future work should therefore be aimed at the elucidation of factors contributing to the variation in drug distribution.

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