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Relationship between antipyrine elimination rate constant, clearance and volume of distribution in the rat

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While the relationship between the inverse of antipyrine half-life and clearance has been shown to be approximately linear in man, a recent report indicated that there was no significant relationship between antipyrine elimination rate constant (λ) and clearance (CL) in the rat. Since this relationship is critical to the use of non-invasive methods to estimate drug metabolizing capacity, we have re-examined the relationship between λ and CL in the rat. A significant correlation ($r = 0{\cdot}887$) was found between antipyrine λ and CL, while only a weak relationship ($r = 0{\cdot}442$) was found between λ and volume of distribution. These data support the use of non-invasive methods to estimate antipyrine elimination in the rat when invasive methods need to be avoided.

Antipyrine has been widely used as an indicator of hepatic oxidative drug metabolism in both animals and man. For both practical and historical reasons, the primary pharmacokinetic parameter reported for antipyrine has been the half-life ($t_{\frac{1}{2}}$). The development of fundamental pharmacokinetic relationships has led to the appreciation that drug clearance (CL) is a more appropriate parameter to measure. Half-life is a hybrid constant dependent upon both CL and volume of distribution (Vd) (Gibaldi & Koup 1981). Thus, changes in $t_{\frac{1}{2}}$ may reflect changes in CL, Vd or both. There are circumstances, however, in which $t_{\frac{1}{2}}$ is more easily measured than CL. For example, in patients where limited blood samples are available, adequate data may not exist to calculate the area under the drug concentration versus time curve accurately (which is necessary to calculate CL accurately and independently). In addition, it is sometimes desirable (or even necessary) to estimate drug elimination through non-invasive methods. Such methods allow estimation of $t_{\frac{1}{2}}$, but not CL.

Recently, the use of antipyrine urinary excretion rate has been proposed as a non-invasive method for estimating antipyrine elimination (Taylor & Blaschke 1984). While urinary excretion data may be used to estimate the elimination rate constant (λ), it is not possible to estimate CL from this method. Unless the predominant factor controlling the variability of antipyrine λ is CL, this method would not provide an accurate reflection of drug metabolizing capacity. Furthermore, this point also holds true for the use of other non-invasive methods of estimating antipyrine elimination, such as breath tests (Rhodes & Houston 1983).

The relationship between $t_{\frac{1}{2}}$, CL and Vd for antipyrine in man has been critically evaluated (Sultatos et al 1980). These investigators found that the relationship between the inverse of antipyrine $t_{\frac{1}{2}}$ and CL was approximately linear. In contrast, there was no significant correlation between $t_{\frac{1}{2}}$ and Vd. Those authors concluded that the use of antipyrine $t_{\frac{1}{2}}$ was a valid parameter for estimating drug metabolizing capacity because CL was the primary source of variability for this parameter. In contrast, it was subsequently reported that there was no significant correlation between antipyrine CL and λ in the rat (Johannessen & Aarbakke 1982). Those investigators concluded that the variability in antipyrine Vd was so great that it was the predominant source of variability in λ. Their data would indicate that, unlike in man, antipyrine λ (or the derived parameter of $t_{\frac{1}{2}}$) is not a valid indicator of drug metabolism in this species. The data also suggest that non-invasive methods of estimating antipyrine elimination may not provide accurate data on drug metabolizing capacity in the rat and reveal possible fundamental differences in the disposition of antipyrine in the rat and man. In view of the implications of this conclusion, we have re-examined the relationship between CL, Vd and λ in the rat.

Materials and methods

The animals in this report were part of a study examining the effect of amiodarone on the pharmacokinetics of antipyrine. Those results will be reported in detail elsewhere. Briefly, male Sprague-Dawley rats, 168–222 g, had an indwelling cannula implanted in the right jugular vein under light ether anaesthesia as described by Weeks & Davis (1964) one day before antipyrine administration. Some animals received pretreatment with amiodarone ($n = 28$) at various doses and for up to five days, while others ($n = 28$) received only vehicle (40% propylene glycol in isotonic saline). Preliminary studies indicated that this vehicle has no significant effect on the pharmacokinetics of antipyrine (unpublished data). On the morning of the study, animals were placed in individual plastic metabolism cages and antipyrine (20 mg kg^{-1}) dissolved in isotonic saline (10 mg mL^{-1}) was infused through the cannula at a rate of 0·34 mL min^{-1}. Serial blood samples (0·25 mL) were obtained through the cannula over 5 or 6 h. Blood was collected in plastic syringes and transferred to heparinized glass capillary tubes. Plasma was separated by centrifugation and stored at −20 °C until analysis by an HPLC method (Svensson 1986).

The plasma concentration versus time data were analysed using non-compartmental methods (Rocci & Jusko 1983). Linear regression of the terminal portion of the curve was used to estimate λ.

Results

Fig. 1 illustrates the relationship between antipyrine CL and λ in 28 control animals. There was a strong correlation between λ and CL (r = 0·887). In contrast, as illustrated in Fig. 2, the correlation between λ and Vd was much weaker (r = 0·442). When the data for amiodarone-pretreated rats were included in the analysis (some regimens of amiodarone significantly reduced antipyrine CL), the correlation between antipyrine CL and λ was slightly greater (r = 0·906, n = 56). Furthermore, when the results for these animals were included in the analysis, there was no significant correlation between λ and Vd (r = 0·233, n = 56). There was no significant correlation between CL and Vd.

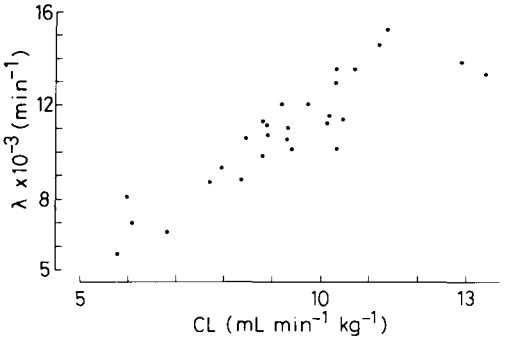

FIG. 1. Relationship between elimination rate constant (λ) and clearance (CL) in 28 control rats. Correlation analysis of λ versus CL demonstrated a significant correlation with r = 0·887

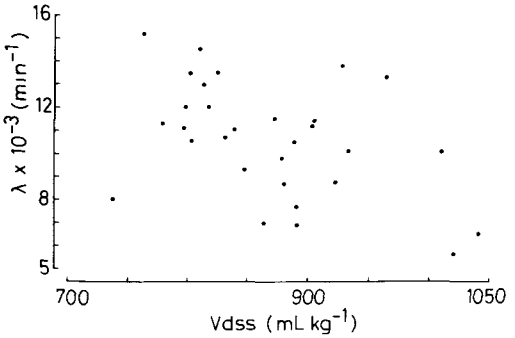

FIG. 2. Relationship between elimination rate constant (λ) and steady-state volume of distribution (Vdss). Correlation analysis of λ versus Vdss demonstrated a weak correlation with r = 0·442

Discussion

The results demonstrate that, as in man, CL is the primary source of variability in λ for antipyrine in the rat. This was also significant under the conditions of pretreatment with an inhibitor of drug metabolism (amiodarone). This observation is particularly relevant since this is the condition in which antipyrine would be used (i.e. to examine the effect of interventions on drug metabolism).

The observation of a lack of correlation between CL and λ made previously (Johannessen & Aarbakke 1982), was probably due to the fact that most CL values in their study fell within a less than two-fold range. In contrast, values in the present study varied over a greater than three-fold range. This may explain the descrepancy between the two studies.

Thus, it is apparent that the antipyrine λ (or the derived $t_{\frac{1}{2}}$) can be used as an indicator of hepatic drug metabolism in the rat, with the indicated limitations described previously (Sultatos et al 1980). Our results would appear to support the use of non-invasive methods of estimating antipyrine elimination in those situations where invasive methods need to be avoided to prevent introduction of additional experimental variables.

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