Simplified approaches to the determination of antipyrine pharmacokinetic parameters

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1 The pharmacokinetics of single intravenous doses of antipyrine were determined in 96 volunteers using multiple (12 or more) plasma antipyrine concentrations measured by high-pressure liquid chromatography during 24–48 h after dosage. These kinetic estimates were compared with those based on: *A*, the 4 h and 12 h points only; *B*, the 4 h through 12 h points; *C*, the 8 h and 24 h points only.

2 Mean clearance values for the complete study (48.0 ml min^{-1}) were nearly identical to abbreviated approaches *A*, *B*, and *C* (49.1, 49.3, and 46.4 ml min^{-1}), and were highly correlated ($r = 0.99$).

3 Coefficients of variation (CV) between individual clearance values for complete vs abbreviated studies averaged 5.5%, 5.8% and 2.9%, and CVs were less than 15% in 95.8%, 93.7% and 98.9% of subjects, respectively, for methods *A*, *B*, and *C*.

4 Overall mean values of elimination half-life (11.9, 12.1, 12.0 and 12.5 h) and volume of distribution (43.7, 45.1, 45.2, and 44.7 l) were likewise very similar for complete *A*, *B* and *C* analyses respectively.

5 The best correlation with the complete study was observed for the 8 and 24 h sampling scheme, for which clearance values were within 5% of the reference method in 84% of subjects, and within 10% in 97% of subjects.

6 Antipyrine pharmacokinetic parameters can be estimated with reasonable precision using a simplified two-point blood sampling procedure following a single intravenous dose. Estimates of elimination half-life, volume of distribution and clearance based on 8 h and 24 h data points correlated best with complete pharmacokinetic studies.

Keywords antipyrine pharmacokinetics abbreviated studies

Introduction

The disposition of a single dose of antipyrine is widely used as an indicator of drug oxidizing activity in humans (Stevenson, 1977; Vesell, 1979; Penno *et al.*, 1981; Branch, 1982; Breimer, 1983; Penno & Vesell, 1983; Vesell & Penno, 1983). Estimation of pharmacokinetic parameters for antipyrine has traditionally required collection

of up to twelve or more blood samples during the 24 to 48 h following administration of a single dose. If antipyrine kinetics could be estimated with reasonable precision using less extensive blood sampling procedures, the utility of this test might be enhanced. Approaches to abbreviated kinetic studies, utilizing fewer blood samples,

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have been reported (Døssing *et al.*, 1982; McPherson *et al.*, 1982; Farrell & Zaluzny, 1984), but the applicability of these approaches to larger populations is not established. The present study evaluated the validity of several abbreviated methods for determination of the pharmacokinetic properties of antipyrine.

Methods

Ninety-six healthy male and female volunteers aged 18 years and above participated after giving written informed consent. Subjects were healthy, active, ambulatory adults, with no history of medical disease and taking no medications. Screening tests included: medical history, complete blood count, laboratory screening profile, and urinalysis.

Subjects received a single 1.0 or 1.2 g intravenous dose of antipyrine administered by a 5 min infusion. Antipyrine was prepared in a sterile aqueous solution (200 mg ml^{-1}), of which 5 ml was diluted to 50 ml with physiological saline and infused into an antecubital vein over a period of 5 min. Venous blood samples were drawn from the contralateral arm into heparinized tubes prior to drug administration, and at the following post-dosage times: 5, 15, 30 min, 1, 2, 3, 4, 6, 8, 12, and 24 h. In some subjects, an additional sample was drawn at 48 h. An indwelling butterfly cannula, kept patent by a slow infusion of normal saline solution, was used to draw blood samples during the first 8 h after the infusion. All other samples were obtained by separate venepuncture. Samples were centrifuged, and the plasma was separated and stored at -20°C until the time of assay.

Analysis

Concentrations of antipyrine in all samples were determined by high-pressure liquid chromatography (Greenblatt *et al.*, 1983). Kinetic variables for antipyrine based on all available data points were determined following iterative nonlinear least-squares regression analysis (Harmatz & Greenblatt, 1987). Data points were fitted to a linear sum of exponential terms (Figure 1). Exponents and infusion-corrected coefficients from the fitted function were used to calculate antipyrine elimination half-life, volume of distribution using the area method, and total clearance (Greenblatt & Koch-Weser, 1975).

Kinetic variables for each subject were also determined based on one-compartment (single

exponential) approximations in the following three ways:

- A. Using the 4 h and 12 h points exclusively;
- B. Using data points between and including 4 through 12 h;
- C. Using the 8 h and 24 h points exclusively.

Correlational analysis was used to compare kinetic results from the complete set of data points with results using each of the abbreviated approaches. Coefficients of variation (CV), between pairs of individual values were determined as the s.d. divided by the mean, expressed in percent.

Results

Based on the complete kinetic studies, mean ($\pm$ s.e. mean) kinetic variables for antipyrine were: elimination half-life, $11.9 (\pm 0.4) \text{ h}$; volume of distribution, $43.7 (\pm 1.0) \text{ l}$; clearance, $48.0 (\pm 2.4) \text{ ml min}^{-1}$. Mean values determined by each of the three abbreviated methods were very similar, and individual values for abbreviated *vs* complete studies were highly significantly correlated (Table 1, Figures 2, 3 and 4). Mean CV values for abbreviated *vs* complete studies were always lowest for the abbreviated approach using the 8 and 24 h points (Table 1). This was further confirmed by evaluating the distribution of individual CV values. CVs *vs* the complete study rarely exceeded 15% for the abbreviated method using the 8 and 24 h points (Table 2). In particular, clearance values using this abbreviated method were within 10% of the reference values in 97% of subjects (Table 2, Figure 4).

Figure 1 Plasma concentrations of antipyrine in a representative subject following intravenous administration.

Table 1 Comparison of kinetic variables for complete vs abbreviated studies

	Elimination half-life (h)	Kinetic variable Volume of distribution (l)	Clearance (ml min ⁻¹)
<i>Complete study</i>			
Mean $\pm$ s.e. mean	11.9 ($\pm$ 0.4)	43.7 ($\pm$ 1.0)	48.0 ($\pm$ 2.4)
$\pm$ s.d.	($\pm$ 3.9)	($\pm$ 9.8)	($\pm$ 23.4)
Range	3.8–26.3	26.0–72.3	19.3–155.1
Median	11.2	44.0	41.6
<i>Abbreviated studies</i>			
4 and 12 h points:			
Mean $\pm$ s.e. mean	12.1 ($\pm$ 0.4)	45.1 ($\pm$ 1.0)	49.1 ($\pm$ 2.5)
$\pm$ s.d.	($\pm$ 4.2)	($\pm$ 11.4)	($\pm$ 24.0)
Range	4.0–26.7	25.7–79.1	17.4–148.4
Median	11.6	44.1	43.8
<i>r</i> *	0.9796	0.9939	0.9959
Mean % CV**	9.6%	5.7%	5.5%
4–12 h points:			
Mean $\pm$ s.e. mean	12.0 ($\pm$ 0.4)	45.2 ($\pm$ 1.1)	49.3 ($\pm$ 2.5)
$\pm$ s.d.	($\pm$ 4.0)	($\pm$ 10.8)	($\pm$ 24.2)
Range	4.0–25.2	25.7–72.6	17.6–160.8
Median	11.6	43.8	43.8
<i>r</i> *	0.9818	0.9950	0.9957
Mean % CV**	10.0%	5.6%	5.8%
8 and 24 h points:			
Mean $\pm$ s.e. mean	12.5 ($\pm$ 0.5)	44.7 ($\pm$ 1.1)	44.4 ($\pm$ 2.1)
$\pm$ s.d.	($\pm$ 4.5)	($\pm$ 10.2)	($\pm$ 19.7)
Range	5.2–30.9	26.2–71.1	17.8–119.6
Median	11.6	45.5	42.3
<i>r</i> *	0.9954	0.9962	0.9983
Mean % CV**	5.1%	4.9%	2.9%

* Correlation coefficient in comparison with complete study.

** Overall mean value of all individual CVs for complete vs abbreviated study.

Figure 2 Relationship between results of antipyrine elimination half-life calculated from the abbreviated approach using 8 and 24 h points and those for the complete antipyrine study. The correlation coefficient is $r = 0.9954$. Dashed line is the line of identity ($y = x$). **Figure 3** Relationship between results of antipyrine volume of distribution calculated from the abbreviated approach using 8 and 24 hour points and those for the complete antipyrine study. The correlation coefficient is $r = 0.9962$. Dashed line is the line of identity ($y = x$).

Figure 4 Relationship between results of antipyrine clearance calculated from the abbreviated approach using 8 and 24 h points and those for the complete antipyrine study. The correlation coefficient is $r = 0.9983$. Dashed line is the line of identity ($y = x$).

Discussion

Attempts to establish the validity of simplified methods for the determination of the pharmacokinetics of antipyrine, lithium, nortriptyline, imipramine, desipramine, chloramphenicol, theophylline and various other drugs have been previously reported (Cooper *et al.*, 1973; Chiou *et al.*, 1978; Brunswick *et al.*, 1980; Slattey *et al.*, 1980; Døssing *et al.*, 1982; McPherson *et al.*, 1982; Farrell & Zaluzny, 1984). Døssing *et al.* (1982) calculated antipyrine clearance based on only a single sample. This method, however, requires that volume of distribution be either simply assumed, or calculated from published equations relating total body water to height, weight, age, and sex. McPherson *et al.* (1982)

used the 4 and 24 h time points after a single oral dose of antipyrine to estimate elimination half-life in patients with obstructive jaundice. Half-life values from the abbreviated study were well-correlated with those using six data points, but intercorrelations of clearance and volume of distribution were not reported. Farrell & Zaluzny (1984) found good correlation in antipyrine clearance values between two-point and six-point studies, but the exclusive use of the oral route for antipyrine dosage, together with use of a one-compartment kinetic model for the six-point study, indicates that even the 'reference' method involves approximation.

In the present study, the reference method for the antipyrine kinetic determination was rigorous, in that antipyrine was administered intravenously, at least 10 sampling points were utilized, the assay method was sensitive and specific, and no approximations were used in kinetic analysis. Furthermore, the sample size was large ($n = 96$). Three different simplified sampling schemes were evaluated in comparison with the complete kinetic study, and all provided good correlation with the reference method. The best correlation with the complete study was observed for the 8 and 24 h sampling scheme. Values of elimination half-life using this two-point scheme appeared to slightly overestimate values using the complete study in subjects whose half-life exceeded 19 h. This indicates a possible deficiency in the approximation approach in subjects or patients with long half-life values. Nonetheless, clearance values based on the 8 and 24 h two-point method were within 5% of the reference method in 84% of subjects, and within 10% in 97% of subjects (Figure 4). The excellent correspondence of the two methods was evident over the entire range of clearance values.

Table 2 Distribution of coefficients of variation

	Fraction of all coefficients of variation (vs complete study)				
	less than 5%	5.0 to less than 10%	10.0 to less than 15%	15.0 to less than 20%	20% or greater
<i>Elimination half-life</i>					
4 + 12 h points	0.34	0.31	0.09	0.18	0.07
4-12 h points	0.31	0.28	0.15	0.18	0.08
8 + 24 h points	0.55	0.30	0.13	0.00	0.01
<i>Volume of distribution</i>					
4 + 12 h points	0.58	0.25	0.11	0.04	0.02
4-12 h points	0.60	0.26	0.08	0.03	0.02
8 + 24 h points	0.61	0.27	0.09	0.03	0.00
<i>Clearance</i>					
4+12 h points	0.57	0.29	0.09	0.02	0.02
4-12 h points	0.58	0.25	0.10	0.02	0.04
8 + 24 h points	0.84	0.13	0.02	0.01	0.00

Thus, antipyrine pharmacokinetic parameters can be estimated with reasonable precision using a simplified two-point blood sampling procedure following a single intravenous dose. Estimates of elimination half-life, volume of distribution and clearance based on 8 and 24 h data points correlated best with complete pharmacokinetic studies.

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