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Data point weighting in pharmacokinetic analysis: intravenous paracetamol in man

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Compartmental analysis of plasma paracetamol concentrations following intravenous injection of 12 mg kg^{-1} in aqueous solution to normal subjects was performed using analogue and digital computer methods. Using a 'simplex' non-linear optimization procedure, the pharmacokinetic parameters were found to be influenced considerably by the choice of the weighting factors (W_i) attributed to individual data points. The plasma half-life of paracetamol varied by up to seven-fold with the weighting factors selected. However, the predicted mean steady-state plasma concentrations were shown to be relatively little affected by the different weighting factors.

Several investigations have recently drawn attention to the need to apply a suitable weighting to individual data points in the non-linear optimization techniques used in pharmacokinetic analysis of experimental data (Mueller & Lieberman, 1970; Albert, Sedman & Wagner, 1974; Boxenbaum, Riegelman & Elashoff, 1974; Kramer, Lewis & others, 1974). All non-linear optimization techniques proceed by attempting to minimize the sum of the weighted deviations (Σd^2) of the n data points (y_i) from the calculated values ($\hat{y}_i$); thus the expression

$$\Sigma d^2 = \sum_{i=1}^{i=n} Wi\,(y_1 - y_i)^2$$

has a minimum value. For replicated values of y_i the reciprocal of the variance of the replicates is an accepted weighting factor (W_i) (Brownlee, 1965), but where replicates are not available the weighting factor cannot be calculated from the data themselves and it is unlikely that any single factor could be universally applicable. The estimates of the pharmacokinetic parameters obtained from non-replicated data for a given set of experimental values vary according to the weighting factor chosen. In this report, we present the pharmacokinetic parameters for paracetamol following intravenous injection into humans, derived from three methods of weighting of the data points.

MATERIALS AND METHODS

Four healthy adult male volunteers aged 28 to 37 years and weighing 68 to 80 kg took part. Paracetamol was given intravenously over 2 min at a dose of 12 mg kg^{-1} as a 1% aqueous solution and venous blood samples were withdrawn from an indwelling cannula into heparinized tubes at frequent intervals for 12 h from the opposite arm. The volunteers had fasted overnight and remained recumbent for 1·5 h after injection. The blood was centrifuged and the plasma stored at −20° until assayed for paracetamol by a g.l.c. method (Prescott, 1971).

The plasma concentration-time curves were fitted by two-compartment and three-compartment open models. Since paracetamol is eliminated primarily by metabolism in the liver and the apparent volume of distribution of the central compartment was found to be quite large, elimination was regarded as occurring solely from this compartment. The initial estimates of rate constants, obtained using an analogue computer and X-Y recorder were used in a simplex non-linear optimization procedure (Nelder & Mead, 1965; Dixon, 1972) which terminated when successive weighted sums of squares agreed within 1×10^{-4}. During optimization, the hybrid rate constants (α, β and γ) were calculated from current transfer rate constants using established equations (Wagner, 1971; Kramer & others, 1974). The algorithms were in Fortran IV in double-precision arithmetic and run on a digital computer. Three weighting factors (W_i) were used:

(i) $W_i = 1$ for all data points.

(ii) $W_i = (\hat{y}_i + y_i)^{-2}$. This weighting factor is recommended (Ottaway, 1973) to avoid bias that can occur if the factors $W_i = (y_i)^{-2}$ or $W_i = (\hat{y}_i)^{-2}$ are used and where the data points span several orders of magnitude. It approximates to the weighting to be used where the coefficient of variation is constant. Replicate analyses of plasma

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samples containing known concentrations of paracetamol showed that the standard deviations were approximately proportional to the concentrations, making this an appropriate weighting factor for non-linear optimization.

(iii) $W_i = (y_i)^{-1.3}$. This intermediate weighting factor was used because in many analytical methods the relation between the variance of replicate measurements (s^2) and the concentration is given by $s^2 = k\,(\text{concn})^m$ where $1 < m < 2$ (Boxenbaum & others, 1974).

RESULTS AND DISCUSSION

With the variance ratio test described by Boxenbaum & others (1974), the results for subjects LP and JN showed that the weighted sums of squares were significantly reduced ($P < 1\%$) when the number of compartments in the open model was increased from two to three. This was not true for the other two subjects for whom the two compartment open model was used. Because of inter-subject differences, weighting factors calculated from the variance of plasma concentrations in the four subjects at each time point (Albert & others, 1974) were not used.

The predicted curves in each subject for two weighting factors $W_i = 1$ and $W_i = (\hat{y}_i + y_i)^{-2}$ were very similar. With the W_i equal to unity, the deviation of each calculated value from the experimental point at the early times is small, but becomes relatively large in the terminal phase, and in comparison with the use of $W_i = (\hat{y}_i + y_i)^{-2}$ this curve fitted the early time-points more closely and the terminal points less well. In general, use of $W_i = (y_i)^{-1.3}$ led to a predicted curve intermediate in position between these extremes.

The pharmacokinetic parameter estimates for each subject, using the appropriate compartmental model, are shown in Table 1, where V_1 is the apparent volume of the central compartment; k_{1j} are the first-order transfer rate constants from compartment i to compartment j; α, β and γ are hybrid rate constants; k_{10} is the elimination rate constant. The steeper slope in the disposition phase of the predicted curve obtained with the W_i equal to unity leads to higher values for Dose/V_1, k_{12} and α. Similarly, the slope in the terminal phase is steeper than that using other weighting factors and leads to higher values of k_{10} and β (or γ).

Although the calculated curves appeared to fit the experimental points for the three weighting factors used, there are large differences in some of the derived parameter estimates (Table 1).

Table 1. *Effect of weighting factor on estimates of pharmacokinetic parameters.*

Subject	Parameter	Weighting factor $W_i = 1$	$W_i = (\hat{y}_i + y_i)^{-2}$	$W_i = (y_i)^{-1.3}$
LP	Dose/V_1	52·7	36·0	33·9
	k_{12}	0·226	0·078	0·083
	k_{21}	0·142	0·071	0·087
	k_{13}	0·011	0·004	0·004
	k_{31}	0·021	0·002	0·002
	k_{10}	0·025	0·013	0·013
	α	0·391	0·158	0·179
	β	0·026	0·008	0·009
	γ	0·007	0·001	0·002
	$t_{\frac{1}{2}}$	1·63	10·3	7·2
	Vd(β)	0·80	3·94	2·93
JN	Dose/V_1	61·5	27·5	29·8
	k_{12}	0·328	0·094	0·103
	k_{21}	0·115	0·112	0·095
	k_{13}	0·008	0·003	0·002
	k_{31}	0·009	0·007	0·005
	k_{10}	0·026	0·012	0·013
	α	0·470	0·213	0·206
	β	0·013	0·010	0·009
	γ	0·004	0·004	0·004
	$t_{\frac{1}{2}}$	2·63	2·75	3·05
	Vd(β)	1·16	1·22	1·36
KY	Dose/V_1	104·1	39·2	47·1
	k_{12}	0·272	0·206	0·119
	k_{21}	0·046	0·108	0·046
	k_{10}	0·045	0·018	0·022
	α	0·357	0·325	0·181
	β	0·006	0·006	0·006
	$t_{\frac{1}{2}}$	1·99	1·99	2·10
	Vd(β)	0·90	0·92	1·00
NW	Dose/V_1	50·9	27·1	27·0
	k_{12}	0·230	0·102	0·063
	k_{21}	0·109	0·129	0·080
	k_{10}	0·023	0·012	0·012
	α	0·356	0·236	0·149
	β	0·007	0·007	0·007
	$t_{\frac{1}{2}}$	1·58	1·71	1·72
	Vd(β)	0·77	0·82	0·83

Dose/V_1 in $\mu g\,ml^{-1}$. Rate constants in min^{-1}. $t_{\frac{1}{2}}$ in h. Vd(β) in litre kg^{-1}.

The half-life ($t_{\frac{1}{2}}$) from the slope ($-\beta/2.303$) of the terminal exponential phase of the semi-logarithmic graph of plasma concentration against time varied by as much as 7-fold with the weighting factor used in the non-linear optimization procedure. Mean plasma half-lives of drug in the four subjects using the factors $W_i = 1$, $W_i = (\hat{y}_i + y_i)^{-2}$ and $W_i = (y_i)^{-1.3}$ were 1·96, 4·19 and 3·52 h respectively.

Plasma half-lives were also determined by linear regression analyses of the terminal points ($n \geqslant 4$) of the semi-logarithmic graphs of plasma concentration against time for 3 subjects. The mean value was 3·37 h. In the other subject insufficient points were found to lie on a straight line and no estimate of the half-life could be obtained by this method.

The mean plasma half-life determined from non-linear optimization with $W_i = (\hat{y}_i + y_i)^{-2}$ was 4·19 h and this presumably represents the best estimate. In previous studies in healthy subjects the paracetamol half-life was usually within the range of

1·5–3·0 h (Brodie & Axelrod, 1948; Carlo, Cambosos & others, 1955; Gwilt, Robertson & others, 1963; Prescott, Sansur & others, 1968; McGilveray, Mattok & others, 1971; Prescott, Wright & others, 1971); in these reports plasma concentrations were measured at only a few times and over relatively short periods of time. Longer half-lives may have been expected in our study since early termination of sampling is a recognized cause of underestimation of the half-life (Gibaldi & Weintraub, 1971). However, in three subjects this was found not to be the case. In one subject (LP) two half-life values fell outside this range but, more importantly, showed considerable variation with the weighting factors used in the simplex non-linear optimization.

The plasma half-life may be used to predict the plasma concentration in the steady state in multiple-dose treatment. Gibaldi & Weintraub (1971) have shown that for a multi-compartment model the mean plasma concentration in the steady state (C_{ss}) is given by

$$C_{ss} = \frac{F.D}{V_{d(\beta)}\beta\tau} \quad .. \quad .. \quad .. \quad (1)$$

where $V_d(\beta)$ is the apparent volume of distribution in the terminal exponential phase and τ is the constant time interval between successive doses.

$V_d(\beta)$ is defined by $V_d(\beta) = V_1/f_1$

where f_1 is the fraction of total drug present in the terminal phase that is in the central compartment.

Since C_{ss} is related to other parameters besides the plasma half-life, the effect of the weighting factor used in the non-linear optimization is not readily predictable. Although the plasma half-life was seen to vary by a factor of up to seven with different weighting factors, Table 2 shows that the predicted mean steady-state plasma concentrations in the four subjects after repeated 4-hourly doses of paracetamol (12 mg kg^{-1}) are very much less variable. In subject LP the reduced variation was due to compensatory changes in the values of the exponential term and $V_d(\beta)$, giving a near-constant product in the denominator of equation 1.

Table 2. *Effect of weighting factor on predicted mean steady-state plasma paracetamol concentrations.*

Weighting factor (W_i)	Plasma concn (μg ml^{-1}) Subject			
	LP	JN	KY	NW
$W_i = 1$	8·85	9·80	9·60	8·88
$W_i = (y_i)^{-1·3}$	10·53	9·76	9·10	8·97
$W_i = (\hat{y}_i + y_i)^{-2}$	11·33	9·70	9·35	9·00

The selection of a weighting factor for these data does not seem to be critical for the prediction of steady-state plasma concentrations.

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