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Problems and Pitfalls in Estimating Average Pharmacokinetic Parameters

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Summary. The problems of obtaining optimal average parameter estimates (APE) from experimental pharmacokinetic data are considered. Four different approaches, three parametric and one non-parametric tests, are compared, using selected individual alcohol concentration data. Pooling the raw data for estimating APE can obscure individual pharmacokinetic characteristics, whereas averaging individual parameter estimates (IPE) exposes unique statistical problems. Furthermore, careful consideration should be given to weighting procedures. The advantages and shortcomings of all four methods are discussed. It is concluded that none can be considered as a universally applicable statistical method in view of the purpose for which the information, derived from a set of data, e.g. an alcohol-kinetic study, is required.

Key words: alcohol-kinetic study; average parameter estimates (APE), individual parameter estimates (IPE), statistical method, pharmacokinetic data

In pharmacokinetics great effort has been put into analytical procedures and into finding kinetic models that define optimal parameter estimates for adequate and precise description of individual data sets, and for relating them to physiological and pathophysiological parameters.

Furthermore, in order to make accurate predictions in any given individual, it is often of the utmost importance to obtain estimates of population characteristics from any routine data of which the pertinent data sets are true samples. It follows, therefore, that pharmacokinetic data analysis not only deals with relating *individual* parameter estimates (IPE) to any particular individual set of data, but also with extrapolating the information to population parameters. Any such procedure bears unique statistical problems, which often are not fully appreciated by the kineticist.

Average parameter estimates (APE) can be obtained by applying least squares nonlinear regression analysis to the total data pool of all individual data sets, using an appropriate model function. Another approach, quite distinct in principle, is to analyse each individual data set separately according to the proposed model function (again using nonlinear least squares) to yield the IPE of the set. In a second step, the IPE are combined to produce the APE. The former method is called the *naive pooled data approach* and the latter method, the *two-stage approach* [1].

We studied the kinetics of ethyl alcohol in 3 different body compartments, arterial blood, venous blood and alveolar air, of 42 healthy volunteers after oral administration of 4 standardized doses of ethanol [2]. Since the blood alcohol concentration was well above the Km of this substance for almost the entire experiment, pseudo-zero-order elimination kinetics, a special form of the more general Michaelis-Menten-type kinetics, with first order absorption, were found adequately to describe the data, i.e.

$$C(t) = C_o(1 - e^{-kt}) - \beta t \qquad \text{Eq. (1)}$$

Four separate approaches (Methods 1, 2, 3, 4) for estimating pharmacokinetic parameters were applied to all the alcohol concentration data using different nonlinear least squares algorithms.

Part of the data was chosen for this paper to illustrate the problems inherent in certain methods for routine pharmacokinetic data analysis and to present alternative approaches to solving these problems.

The results obtained by the four analytical methods are compared and their advantages and shortcomings or pitfalls are discussed.

General Approach to Summarizing Individual Kinetic Data

1. Parametric Analysis of the General Response Function

Any kinetic experiment can be characterized by a general input function $y_i(t)$ and a response function $Y_i(t)$ in such a way that

$$Y_i(t) = f_{(p_{1,i}, \ldots, p_{n,i})} y_i(t) \qquad \text{Eq. (2)}$$

where f is the linear or nonlinear operator (e.g. Bateman function), *p* are the parameters (fixed and random), $p_{k,i}$, for $k = 1,2,\ldots n$.
For the unit impulse function, i.e. Dirac's δ-function,

$$y(t) = \delta(t) \qquad \text{Eq. (3)}$$

let the response function be given, for example, by

$$Y(t) = a \cdot e^{-\beta t} \qquad \text{Eq. (4)}$$

In case of a linear operator the general response function is then determined by the convolution

$$Y(t) = a \int_0^\infty y(t-t') e^{-\beta t'} dt' \qquad \text{Eq. (5)}$$

When n experiments are carried out under the same standardized conditions, there is a tendency to summarize the results in order to draw conclusions about important common characteristics using the average result, and to obtain an estimate of interexperimental variation as well as residual variances. Therefore, any set of n response functions of the general type such as Eq. 5 can be characterized by:

1.1. *the arithmetic mean curve* of all individual curves

$$\mu\{Y(t)\} = \frac{1}{n} \sum_{i=1}^{n} Y_i(t) \qquad \text{Eq. (6)}$$

and their variance curves:

$$v\{Y(t)\} = \frac{1}{n} \sum_{i=1}^{n} (Y_i(t) - \mu\{Y(t)\})^2 \qquad \text{Eq. (7)}$$

which we may call *"pooled average functions"*, or

1.2. *the average parameter curve,* after averaging all equally indexed IPE of the experiments. The *two-stage approach* first determines the IPE, e.g. $p_{k,i}$, and in a second step averages the n IPE to obtain the APE:

$$\mu\{p_k\} = \frac{1}{n} \sum_{i=1}^{n} p_{k,i} \cdot w_{k,i} \qquad \text{Eq. (8)}$$

where $w_{k,i}$ are statistical weights, depending on the parameter index k and the test index i. Those functions will be called *"parameter average functions"*.

The pooled data approach, which leads to the pooled average function, is always possible and in its strict sense plausible.

The *two-stage* approach yielding the parameter average function is meaningful only when the following criteria are satisfied:

1.2.1. All individual data sets can be represented adequately by the same model function.

1.2.2. The null hypothesis for the distribution of all equally indexed IPE has to be satisfied, i.e. all n functions of the set are true samples of the same population with normal parameter distributions.
When the prerequisites 1.2.1. and 1.2.2. are not applicable, weighted parameter averaging is not strictly correct.

To illustrate the absurdity of parameter averaging under unsuitable conditions let us assume the following unit impulse response functions:

$$\Phi_1(t) = a_1 \cdot e^{-\beta_1 t} \qquad \text{Eq. (9)}$$

$$\Phi_2(t) = a_2 \cdot e^{-\beta_2 t} \qquad \text{Eq. (10)}$$

for $a_1 = 4.0$, $a_2 = 3.0$, $\beta_1 = 0.5$ and $\beta_2 = 2.0$.

These two functions are shown in Fig. 1 together with the pooled average, the parameter average and the "characteristic parameter" (cf Section 3) curves. It is clear that the parameter average curve is far from the other averages and, in fact, is quite unrealistic.

In order to avoid inadequate averaging we propose the following considerations and procedures:

a. For a series of experiments input functions (e.g. i.v. doses) of the same type should always be employed, e.g. impulse functions or step functions.
b. The response is measured in adequate time intervals until the response function can be approximated by its asymptotic behaviour.
c. A nonlinear least squares fit gives an estimate of the adequacy of the model function and the accuracy of the parameter estimate of that function.

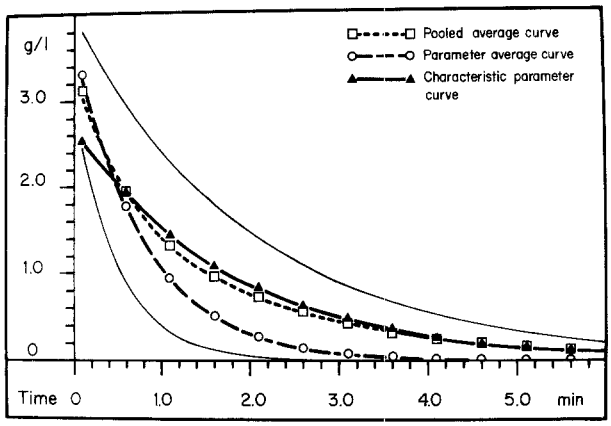

Fig. 1. Demonstration of the inadequacy of the parameter average curve in a case where the two individual curves (full lines) exhibit very different shapes despite identical analytical representation. Curve □. represents the *pooled average function*, ○. the *parameter average function*, and ▲. which represents the *average response function* is calculated with the "characteristic parameters"

d. Adequate resulting curves, according to chi-square tests, are weighted, where the weight function takes into account both the root mean square (rms) fitting error and standard deviation, i.e. the a priori estimate of the measurement error.
e. Averaging of the adequate weighted model function yields the *average response function,* which is a phenomenological description of the typical response function of each single set of data that follows the model function.

This *average response curve* need not necessarily follow exactly the model function, but it can be characterized on a model free basis with moments and cumulants [3, 4, 5].

2. Nonparametric Analysis of the General Response Function Using Moments and Cumulants

When a dose is instantaneously introduced into the body, Eq. (4) describes the drug concentration (Y(t)) at any given time t.

In the following formalism, Y(t) can be any drug concentration as a function of time which may result from a specified "drug input" procedure, provided that the following conditions are satisfied:

- the time of incorporation and the total dose administered in this time must be finite,
- Y(t) must be zero for all times $t<0$, apart from a possible equilibrium concentration $Y_0=\text{const.}$, which would have to be subtracted from Y(t),
- Y(t) must vanish for $t\to\infty$: in fact asymptotically Y(t) must vanish more rapidly than exp. $(-\alpha t)$, where $0<\alpha<\infty$.

Under these conditions Y(t) can be described by the methods of moments and cumulants [4, 5] analogous to methods applied in mathematical statistics to frequency distribution functions. Moments and cumulants are measures of area, location and shape of functions of the class defined above. The l^{th} moment ($l=0, 1, 2, \ldots$) of Y(t) is defined by Eq. (11),

$$M_l(Y(t))=\int_0^\infty t^l Y(t)dt \qquad \text{Eq. (11)}$$

The response function Y(t) has a Laplace transform $\bar{Y}(s)$ which can be written:

$$\bar{Y}(s)=\int_0^\infty Y(t)e^{-st}dt=\sum_{l=0}^{\infty}\frac{(-s)^l}{l!}M_l \qquad \text{Eq. (12)}$$

$$\text{where } M_l=\int_0^\infty t^l Y(t)dt \text{ (i.e. } l^{th} \text{ moment)} \qquad \text{Eq. (13)}$$

$$\text{and } \bar{Y}(s)=\exp\left\{\sum_{l=0}^{\infty}\frac{(-s)^l}{l!}C_l\right\} \qquad \text{Eq. (14)}$$

where C_l is the l^{th} cumulant

The convolution of two functions, cf. Eq. (5), leads to a function whose cumulants are the sum of the respective cumulants of the functions to be convoluted. Therefore, in a linear model, the unit impulse response function can be obtained from the response function to a general input function by simply subtracting the C_l of that input function from the C_l of the observed response function.

An analogy can be drawn from physical engineering to illustrate the significance of moments and cumulants.

The zero, first and second moment in relation to the origin of the function Y(t) correspond to the weight, the torque and the moment of inertia, respectively, of the area under the Y(t) vs. t curve. For higher order moments there is no such analogy.

The zero cumulant equals the logarithm of the zero moment, the first and second cumulants are the abscissa of the centre of gravity of Y(t) and the central moment of inertia, respectively.

3. Combination of Parametric and Nonparametric Analysis

For any average response function one can find values of the parameters that characterize the model function, such that the first moments of the associated model function exactly match the first moments determined from the average response function. We shall call them the "characteristic parameters". Furthermore, the characteristic parameters, which are derived from the weighted average response curve are always meaningful, even when the points 1.2.1.

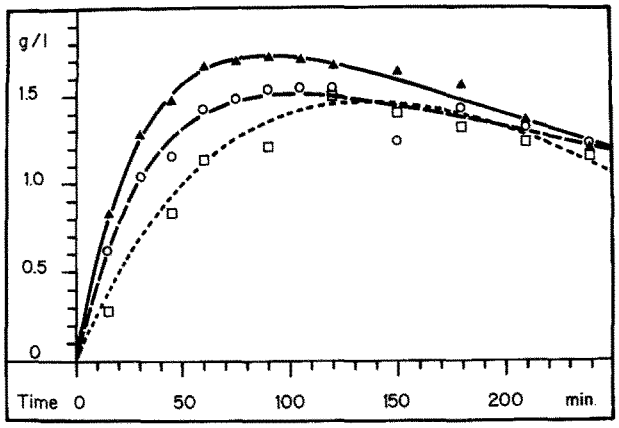

Fig. 2. Blood alcohol concentration [g/l] vs time [min] after p.o. administration of ethyl alkohol 1.25 g/kg body weight at time 0. ▲ Subject 007; ○ 008; □ 011

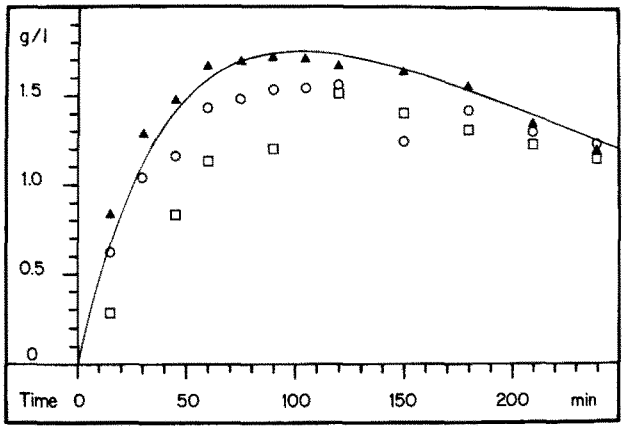

Fig. 3. Blood alcohol concentrations [g/l] vs time [min] in subjects 007 (▲), 008 (○) and 011 (□) as shown in Fig. 2. The curve corresponds to the unweighted average parameter estimates (APE) as given in Table 1. Unweighted averaging in this case has led to a paradoxical "average" curve

and 1.2.2. do not hold true. In practice, the computation of moments has to be restricted to a finite upper limit of time, or the integrations have to be extrapolated into the asymptotic region extending to infinity.

Methods and Results

Ethanol Concentration Time Profiles as an Example of Typical Pharmacokinetic Data:

Parametric Evaluation (Two-Stage Approach)

Unweighted Parameter Averaging. The individual data sets from 3 subjects (Nos 007, 008 and 011) from the dosage group ethanol 1.25 g/kg have been chosen to exemplify and illustrate the problems in analysing pharmacokinetic data mentioned in the introduction.

Table 1

Methods/estimates		Individuals from Fig. 2			Average parameter estimates:
Fit: SAAM program		007 ▲	008 ○	011 □	(unweighted) Fig. 3
rms resid. conc.	[g/l]	0.07683	0.0386	0.0984	0.21
C_o	[g/l]	1.89	2.20	3.30	2.46 ±0.43
k	[h^{-1}]	1.74	1.97	0.67	1.46 ±0.40
β	[g/l·h]	0.170	0.239	0.489	0.299±0.097
C_{max} (calcul.)	[g/l]	1.50	1.73	1.47	1.75
C_{max} (observ.)	[g/l]	1.54	1.71	1.54	1.60 ±0.07

In a first step the IPE (C_o, k, β), which describe the proposed model function, Eq. (1), were estimated according to the Gauss-Newton criterion using a nonlinear least squares regression program (SAAM-25) on a UNIVAC-1108 digital computer [6]. The individual plasma concentration – time curves of the 3 subjects are presented in Fig. 2.

In a second step the unweighted APE ($\bar{C}_o$, $\bar{k}$, $\bar{\beta}$) were obtained by taking the arithmetic mean of the three sets of IPE. Unweighted averaging of the IPE, which yielded the APE, occasionally resulted in paradoxical model functions in which some average time-concentration curves reached a higher peak concentration than the maximum concentration values observed in the corresponding individual experiment. All individual data points and the resulting average plasma concentration curve are shown in Fig. 3, constructed with the computed unweighted APE values.

The results thus obtained were analysed in the following way: The optimum IPE were checked using MARFIT, a nonlinear least squares regression program of the MARQUARDT type; Tables 1 and 2 show excellent agreement of the results obtained by this program with those from other program the (SAAM-25). In addition, through interactive simulation MARFIT permits visualization of the model function and the individual data points on a CRT, a quasi-analog simulation. This reveals optimal starting conditions for the digital optimization procedure of the MARQUARDT algorithm.

Fitting the data to the proposed model function in this way, it was possible to demonstrate that by correlated changes in the parameter values, almost as good an adjustment could be obtained, satisfying the Gauss criterion, with rather different IPE.

The MARFIT program provides the sum of squares of the deviations from the fitted curve as well as the standard deviations of the IPE, determined

Table 2

Methods/estimates	Individuals from Fig. 2			Average parameter estimates:
Fit: MARFIT Prog.	007 ▲	008 ○	011 □	(weighted) Fig. 4
rms resid. conc. [g/l]	0.07681	0.0385	0.0963	0.045
$C_o \pm \sigma_{C_o}$ [g/l]	1.881 ±0.15	2.199 ±0.065	3.272 ±1.21	2.15 ±0.06
$k \pm \sigma_k$ [h^{-1}]	1.765 ±0.25	1.964 ±0.110	0.669 ±0.23	1.72 ±0.09
$\beta \pm \sigma_\beta$ [g/l·h]	0.168 ±0.49	0.239 ±0.020	0.483 ±0.24	0.241 ±0.020
C_{max} (calcul.) [g/l]	1.50	1.72	1.46	1.63
$g_{C_o} = 1/\sigma^2_{C_o}$	44	237	1	282
$g_k = 1/\sigma^2_k$	16	83	19	118
$g_\beta = 1/\sigma^2_\beta$	4	2500	17	2521

Table 3

Chi-square Test of Parameter Distribution	C_o	k	β
χ^2	4.6	26.0	1.05
p (χ^2)	0.1	0.001	0.6

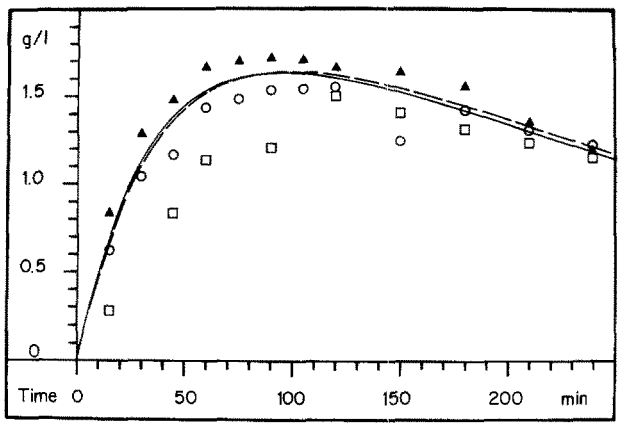

Fig. 4. Blood alcohol concentrations [g/l] vs time [min] in subjects 007 (▲), 008 (○) and 011 (□) as shown in Fig. 2. The full curve corresponds to the weighted average parameter estimates (APE) as given in Table 2. The dashed curve corresponds to the "characteristic parameter" values as described in text. Both curves agree within the confidence limits and represent credible estimates of average blood alcohol concentrations vs time under the conditions employed. The bad representation of the observations for subject 011 is due to the very large standard deviations of those IPE, as can be seen in Table 2, i.e. to extremely unreliable observations in this case

from the linearized error propagation of the individual fit deviations (Table 2). These were of such different magnitude that simple parameter averaging resulted in the "paradoxical" average concentration curve of Fig. 3, while strictly weighted parameter averaging yielded the more realistic curve of Fig. 4.

Weighted Parameter Averaging. The results of the unweighted APE and strictly weighted APE, together with the σ and rms-residuals are presented in the last columns of Tables 1 and 2, respectively, where the reciprocal values of the respective variances of the IPE served as the weighting functions (Table 2).

Using the chi-square test to examine the distribution of the IPE, no significant differences were found between the parameters Co and β, whereas the null hypothesis of a normal k-distribution had to be rejected (Table 3). Thus, weighted averaging of the IPE with respect to k did not seem to be advisable, and unweighted averaging of the individual k-parameters appeared preferable.

Weighted Averaging of the Individual Parameter Vector. IPE and the APE will be considered as vectors with components Co, k and β according to the model described by Eq. (1).

Any sample of random variable vectors ($x_1, \ldots x_i, \ldots x_p$) from a homogeneous population of such vectors can be characterized by the sample mean vector $\bar{x}$ and its covariance matrix. This sample mean vector and the covariance matrix of a sample of multivariate normally distributed random variable vectors permits estimation of all pertinent parameters of this distribution. In this sense the terms IPE and APE are defined as stated above.

It is important to realize that four basically different parameter covariance matrices (PCVM) must be distinguished:

1. The intra-experimental PCVM, pertinent to a single set of data, is calculated from the stochastic error propagation by the final step of the optimization procedure. It does not permit any estimate of distribution or of the correlation of parameters between individual data sets.
2. The inter-experimental PCVM.
3. The total PCVM of the sample, and
4. The covariance matrix of the AP-vector.

The IPE were obtained by a standard nonlinear least squares procedure using Eq. (1) and the MARQUARDT algorithm on all alcohol concentrations measured in one individual. The standard deviations of each IPE component, as well as the correlation coefficients between each pair of them, represent important measures of the reliability of the IPE, and are essential in view of the adequate averaging process leading from the different IPE to the APE of the set.

The APE of any particular set has been obtained by weighted averaging of all IPE from the set. In view of the significant (computational) correlations between IPE components, weighted averaging must not be applied separately to each IPE component, but to the IPE vector as an entity. An appropriate statistical weight attributable to each IPE vector is given by the reciprocal of the total variance; total variance means the trace of the IPE covariance matrix or, in other words, the sum of squares of the standard deviations of all the components of the IPE vector. The adoption of this type of statistical weight is a simple, yet efficient approximation, compared to more sophisticated merging procedures. It emphasizes IPE of a particular type, which exhibits a particularly small standard deviation of all the components, while it gradually decreases the influence on the APE of such IPE with one or more components and a larger standard deviation.

This estimate of statistical weights attributed to the IPE vectors would be improved if the parameters had previously been standardized. This is inconvenient, however, as all optimizations must be repeated when new cases are added. The omission of standardization is usually tolerable, as "ill conditioned" optimizations tend to exhibit markedly increased variances of all parameters. Still, caution regarding this point is necessary. Doubtful cases should be eliminated rather than incorporated in weighted averaging.

The statistical reliability of the APE so obtained is again characterized by a standard deviation of each APE component, as well as by correlation coefficients for each pair of them. It should be kept in mind that standard deviations of APE components indicate statistical uncertainties of the estimated parameter averages rather than fluctuations between parameters attributable to different individuals of the set.

2. Non-parametric Evaluation (Moment Analysis, see page 597)

The average response function (dashed line) calculated from moments and cumulants is shown in Fig. 4. The following values for the parameters that characterize the model function (characteristic parameters) have been obtained by this program:

$C_o = 2.18\ g/l$
$k = 1.63\ h^{-1}$
$\beta = 0.24\ g \cdot l^{-1} \cdot h^{-1}$

Discussion

Method 1

Averaging the unweighted IPE in order to obtain the APE, which are estimates of the population pharmacokinetic parameters, yielded a paradoxical result, of which a typical example is shown in Fig. 3, with the average plasma concentration curve exceeding the highest measured data point.

There might, therefore, be great uncertainties in APE, as observed in the present example. Analogue computation in order to find optimal starting conditions for digital iteration procedures can yield entirely different parameter values, which satisfy the Gaussian optimization criterion equally badly.

Unweighted averaging of the IPE, however, certainly does not neglect *interexperimental differences* by giving equal weight to all the individual data sets.

It is important, therefore, to have a good estimate of the a priori measurement error, e.g. the standard deviation (σ), and to examine the standard deviations of IPE, as the optimization procedure might greatly enhance the measurement errors. Doing this can help to eliminate the worst cases of almost "faulty individuals".

In forensic medicine this type of information might be crucial in predicting individual alcohol concentration-time profiles, as in defending a deliquent, who might be an "extreme case" in respect to population alcohol kinetics.

Method 2

Weighting the IPE independently weakens the influence of the IPE on the APE with a rather large standard deviation. Such a procedure eliminates the observed paradoxical results, but brings statistical problems that often are not appreciated in their full extent. We found in our example that, using chi-square to test the parameter distribution, at least the first order absorption rate constant (k) did show skewness and kurtosis in such a way that "simple" weighting procedures did not seem meaningful.

An alternative approach in estimating average or population kinetic parameters is to pool all individual data and analyse it all together by means of nonlinear least squares (naive pooled data approach).

This approach carries several important problems, which need to be carefully watched when using this method:
1. It totally ignores individual pharmacokinetic characteristics and, by doing so, might therefore obscure or loose important information on how the body handles physiological or xenobiotic substances.
2. It cannot differentiate interindividual, intraindividual and residual variances, although they contribute to a varying degree to the total variance, since all deviations of fit are pooled in one single error term. This is an important drawback of the method and explains in part the shortcomings of Point 1.
3. It is well known in pharmacokinetics that average concentration curves derived either by averaging IPE to get APE, or directly by the "naive pooled data approach", do not necessarily have to follow the typical individual model function. Undefined statistical uncertainties and large "unknown" interindividual variations might "smooth" the average response curve in an unpredictable way. Uncritical and false emphasis might therefore be given to fortuituous findings when individual pharmacokinetics and careful error analysis are ignored. We did not use this method.

Weighted, independent averaging of the individual IPE, using the reciprocal value of the respective variances as statistical weighting functions, emphasizes the individuals with apparently precise parameter values. It, therefore, might depress inter-individual variation in an uncritical manner. This would be a considerable drawback in situations where the contribution of the inter-individual variance to the total variance is of utmost importance, as it often is in medicine, whereas the reliability of the individual parameter mean values or average concentration curve is less in doubt.

Appreciating this problem, two alternative methods were tried to solve the paradoxical results obtained with Method 1. It was the intention to use the data to predict individual kinetics of ethyl alcohol.

Method 3

In this approach weighting was applied not to every individual parameter separately, but to the individual parameter vector, with the components C_o, k and β as an entity, according to the reciprocal value of the trace of the intraexperimental covariance matrix.

This method eliminates the extremes and shortcomings of Methods 1 and 2, but it also depresses the inter-individual variation to a certain extent and in this way loses the advantage of Method 1.

Careful consideration of correlated uncertainties of IPE components, e.g. by application of the described *weighted averaging*, is strongly recommended for the following reasons: The statistical uncertainties of the IPE do not only depend on the magnitude of statistical errors of the concentration measurements, but particularly on the configuration of the deviation from the fit in each case. Due to inherent properties of both the model function and the Gauss' fitting criterion, one cannot intuitively appreciate the magnitude and sign of correlated error propagation. With very similar magnitudes of experimental errors the corresponding standard deviations of the IPE components may vary by as much as an order of magnitude. Only the careful computation of this effect in the course of optimising the fit can help to avoid the inclusion of extremely unreliable individual parameter estimates in the averaging procedure which leads to the APE.

Method 4

Method 4 is basically a nonparametric analysis, using moments and cumulants to characterize the individual ethanol concentration data. The first 4 moments and their corresponding cumulants, together with a parametric model, are used to find the *"characteristic parameters"* of the average response function, which reflect a phenomenological description of the proposed model function.

We consider that the "method of characteristic parameters" reliably gives the true parameter mean values, and it is appropriate therefore, when mean values are of primary interest. We have compared a direct integration method, which is less sensitive to scatter, with analytical integration of model functions obtained from the optimization procedure, using the same weight function as in Method 3, and found comparable results.

At present Method 4 is not set up for estimating intra-individual variation, since it has been used to obtain good individual parameter estimates. It is hoped, however, that the method can be extended in this way by further development of its theory and generalization of the pertinent algorithms.

Conclusions

When the four different methods are compared the following conclusions can be drawn:
1. The four Methods (1, 2, 3 and 4) yielded comparable estimates of the average kinetic parameters $\overline{C}_o$, $\overline{k}$ and $\overline{\beta}$, but with different standard deviations.
2. Apart from different values of reported estimates and variances, the information obtained by the different analytical methods should be judged in rela-

tion to its particular properties and its intended use.

It is concluded, therefore, that, before designing an experiment the kineticist should carefully consider the purpose for which the results will finally be used. By choosing the appropriate statistical methodology for data analysis, the results will be more accurate and more reliable.

The statistical problems of pharmacokinetic data analysis are now being appreciated more often than formerly and alternative methods of estimating population pharmacokinetic parameters [1, 7] have been elaborated, especially for dealing with routine clinical pharmacokinetic data.

NONMEM, Nonlinear Mixed Effect Model, a recently developped computer program [7, 8] for estimating population pharmacokinetics from routine patient data, simultaneously takes care of all the parameters of the model, including the variance parameters. It carefully analyses the variances of the total error, i.e. the intra- and interindividual variation, inadequate pharmacokinetic modelling, analytical error and residual error, using a method called extended least squares. This program seems to avoid the shortcomings of both "standard" methods, the naive pooled data approach and the two-stage approach. It provides accurate and precise estimates of all pertinent parameters and computes their confidence intervals [1, 7, 8, 9].

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