Model-Free Evaluation and Mean-Time Concept in Pharmacokinetics

D. Brockmeier

Hoechst AG, Klinische Forschung, H840, 6230 Frankfurt/M-80, FRG

SUMMARY

Pharmacokinetic characteristics may be separated into three classes: firstly, those which are truly independent of pharmacokinetic modelling - curve characteristics for instance, such as C_{max} or t_{max} but also organic clearance values; secondly, those which can be evaluated without an explicit pharmacokinetic model but under basic assumptions - characteristics such as total clearance, mean and variance of residence times or total volume of distribution; and thirdly, those which are bound to elaborate pharmacokinetic models, such as hybrid constants, micro-constants or partial volumes of distribution.

It can be demonstrated that the second class - the model-independent evaluated characteristic - and the third are mutually transferrable; examples of this transcription are given. However, these purely theoretical considerations can only demonstrate that the second class is consistent with classic pharmacokinetic modelling.

The usefulness of the model-independent evaluated characteristic is underlined by results of clinical pharmacological investigations in which this technique was applied. The topics addressed by these studies cover the problems of deep compartments, differences in absorption, influence of disease, drug interaction, and first-pass metabolization.

Since the mean-time concept in particular is still controversial in the literature, some general theoretical explanations seem to be necessary.

Key words: Mean residence time - Compartmental models - Deep compartments - Mean absorption time - Site-dependent absorption - Renal insufficiency - Intestinal clearance - First-pass effect

INTRODUCTION

Pharmacokinetics as a service contributes to the overall picture of a drug, characterizing the pharmacological, toxicological, and pharmaceutical properties of that substance. During drug development, a large number of detailed pieces of information are compiled, each of which may provide the answer to one part of the puzzle which makes up the overall picture. It is a subject of discussion whether this partial aspect is important or even decisive to the overall picture in individual cases. It is also debatable whether this part has to be filled with very complex interpretations as physiological models (1) or with apparently very simple models as the statistical interpretation of the fate of drugs in the body (2). The following demonstrates how this part of the puzzle is completed by means of the mean-time concept, in full consideration of the fact that there are other parts to which it is linked.

Theoretical background

Some notes concerning the nomenclature are necessary; the mean residence time and the moments of residence times in general are defined by a complex integral formula (3):

$$m_k = \frac{{}_0\int^{\infty} t^k \, dM(t)}{{}_0\int^{\infty} dM(t)} \qquad \text{Eq. 1}$$

where dM(t) is an infintesimal amount of drug definitely leaving the system at time elapse t after administration (4). The implications when looking at residence times

- or rather, transit times - from the endpoint «eliminated» has been discussed elsewhere (4,5).

However, a numerical approximation is shown in Equation 2 (6):

$$m_k = \frac{\sum (t_i)^k \cdot \Delta M(t_i)}{\sum \Delta M(t_i)}$$

Eq. 2

where $\Delta M(t)$ means the fraction of the drug definitely leaving the body during the period Δt for which t_i is the midpoint. $\Delta M(t)$ may be a measured or a predicted quantity. The outcome of Equation 1 or the approximation Equation 2 is explained in Table 1.

In contrast to mathematical statistics a zero moment m_o is defined as the area under the curve AUC which may be estimated by the area under the data AUD using the trapezoidal rule. In mathematical statistics the zero moment must always equal unity (3); however, here it is more convenient to define a zero moment different from unity. The first moment m_1 is the arithmetic average of all life-spans any one of the molecules spends in the body system (2). The second moment around zero m_2 is nothing more than a mathematical definition. The second central moment μ_2 is simply better known: it is the same as the second moment around the mean - called the variance of residence times. In the same way, the third moment around the mean is what is referred to as the skewness of the distribution of residence times of drug molecules in the system.

What is really fascinating with this statistical interpretation of pharmacokinetics is the hierarchical order of the information, increasing with each moment involved in the interpretation. This is summarized in Table 2.

TABLE 1. Definitions used for the statistical interpretation of the fate of drug in the system

m_o	AUC	zero moment of residence times
m_1	MT_{total}, MRT	first moment or mean of residence times
m_k		k. th moment of residence times
μ_2	VT_{total}, VRT	second central moment or variance of residence times
μ_3	ST_{total}, SRT	third central moment or skewness of residence times

where $\mu_2 = m_2 - (m_1)^2$

$\mu_3 = m_3 - 3 \cdot m_1 \cdot m_2 + 2 \cdot (m_1)^3$

TABLE 2. Hierarchy of the information collected by the statistical interpretation of the fate of drug in the system

Model-independent evaluable or global characteristics		Evaluable compartmental model
m_o	CL_{total}	
	CL_{total}/f	
& m_1	MT_{vss}, V_{ss}	1-CP
	MT_{sys}, V_{sys}/f	
& m_2		1-CP-ABS
& m_3		2-CP

where 1-CP means one compartment body model, 1-CP-ABS means one compartment body model with first order absorption, and 2-CP two compartment body model.

As is well known, the area under the curve gives the total clearance or total clearance over f (2), from which one may derive the dosing schedule. Clearance explicitly reflects the overall properties of the drug and it is not necessary to state a model.

In adding the first moment, one is in the position to split up total clearance into its two components - volume and time. These components are the mean residence time and the steady state volume of distribution in the general case. It seems worth noting that the mean time offers a characteristic which is suprerior to the biological half-life or the dominant half-life (7) and other attempts which have been undertaken to give an overall characteristic of drug elimination, since the total mean time weights each exponential process according to its contribution to the area under the curve (8).

The steady state volume of distribution shows the volume which can be reached by drug molecules. This may be accessible to physiological interpretation or may simply show that the drug is accumulated somewhere in the body.

A one-compartment model can be defined by the zero and the first moment - if reasonable:

$$k_e = \frac{1}{MT_{vc}} = \frac{1}{m_1}$$

Eq. 3a

$$C_o = \frac{D}{V_c} = \frac{AUC}{MT_{vc}} = \frac{m_o}{m_1}$$

Eq. 3b

where k_e is the rate constant of elimination, MT_{vc} is the mean time in the system, *i.e.* a single volume of distribution V_c. D denotes the dose administered and m_1 is identical with MT_{vc}. A Bateman-function can be defined by adding the second moment (8,9); of course, this is reasonable after non-systemic administration provided the Bateman curve describes the concentration time course adequately:

$$k_{e/a} = 1/\left(\frac{m_1}{2} \pm \sqrt{\frac{m_2}{2} - \frac{3 \cdot (m_1)^2}{4}}\right)$$

Eq. 4a

$$f \cdot C_o = \frac{f \cdot D}{V_c} = AUC \cdot k_e = m_o \cdot k_e$$

Eq. 4b

where k_a means the rate constant of absorption and k_e has the same meaning as above. From Equation 4a it is obvious that it is impossible to decide from the concentration time curve alone which process reflects absorption and which elimination.

A two-compartment model can be described when the third moment is annexed (8), again under the logical presumption that the concentration-time course can be adequately described by two exponentials:

$$\lambda_{1/2} = 1 \Big/ \left(\frac{m_3 - 3 \cdot m_1 \cdot m_2}{6 \cdot m_2 - 12 \cdot (m_1)^2} \pm \sqrt{\left(\frac{m_3 - 3 \cdot m_1 \cdot m_2}{6 \cdot m_2 - 12 \cdot (m_1)^2} \right)^2 + \frac{3 \cdot (m_2)^2 - 2 \cdot m_1 \cdot m_3}{6 \cdot m_2 - 12 \cdot (m_1)^2}} \right)$$

Eq. 5a

$$C_1 = \frac{m_1 - (1/\lambda_2)}{(1/\lambda_1) - (1/\lambda_2)} \cdot m_0 \cdot \lambda_1$$

Eq. 5b

$$C_2 = \frac{m_1 - 1/\lambda_1)}{(1/\lambda_2) - (1/\lambda_1)} \cdot m_0 \cdot \lambda_2$$

Eq. 5c

where λ_1 and λ_2 are the hybrid rate constants and C_1 and C_2 are the intercepts for the two exponential functions.

It is therefore possible to proceed from a simple characterization - for instance by clearance, mean time, and volume of distribution - to more complex interpretations by adding higher moments without dropping the former ones.

As a reminder, the equations for the model-independent *evaluable* pharmacokinetic characteristics are listed below:

Total clearance CL_{tot} or relative total clearance CL_{tot}/f is the quotient of the dose administered D and the area under the curve AUC (2). AUC can be substituted by the area under the data AUD with or without an extrapolation.

$$\left.\begin{matrix} CL_{tot} \\ CL_{tot}/f \end{matrix}\right\} = \frac{D}{AUC} = \frac{D}{m_o}$$

Eq. 6

With intravenous bolus injections, the steady state volume of distribution V_{ss} is the product of total clearance and the mean of times for which the molecules linger in this volume. In all other cases, *i. e.* nonsystemic and non bolus administration, the respective product gives the relative total volume of distribution V_{sys}/f, which may even include a site of absorption or release (10).

$$\begin{matrix} V_{ss} = CL_{tot} \cdot MT_{vss} \\ V_{sys}/f = CL_{tot}/f \cdot MT_{vsys} \end{matrix}$$

Eq. 7

The mean time can be obtained from the concentration-time-data by two consecutive integration steps (11). Numerical integration of the concentration time course yields a series of AUD data depicted in the lower graph of Figure 1.

In the second numerical integration step the area between the curve and its asymptote is determined, and the mean is estimated as ABC over AUC (11).

$$\left.\begin{matrix} MT_{vss} \\ MT_{vsys} \end{matrix}\right\} = \frac{ABC}{AUC}$$

Eq. 8

Applications

Some practical examples will be presented which show that essential information can be obtained from clinical trials using the model-independent approach to evaluation; results from our own work have been balanced with examples taken from literature. Nevertheless, this can only illustrate a small section of the

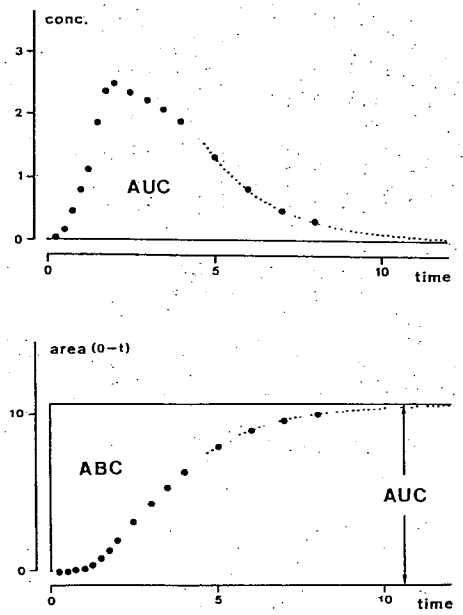


FIG. 1. Schematical presentation of the assessment of the total mean time by the rule of «ABC over AUC». The analytical integration can be substituted by the two sequential numerical integration steps including an appropriate exponential extrapolation.

applications of model-independent characteristics in clinical pharmacology.

In 1980 von Hattingberg *et al.* published a paper on the pharmacokinetic characteristics of gentamicin (12) which were derived by model-independent evaluation techniques using data from Wahlig and coworkers (13). The mean residence time and the terminal half life were estimated from urinary data alone, which also indirectly served to estimate the steady state volume of distribution. The results are compared with data published by Schentag and colleagues (14) in Table 3.

Schentag and his colleagues used data from 47 patients (16 with normal renal function) treated with 0.4 to 7 mg/kg/day for 5 - 45 days. With the cumulative effect of repetetive dosing and an improved analytical method, they were able to demonstrate the existence of a deep compartment and to explain why previous investigators had employed only a one-compartment model for gentamicin kinetics.

Comparing the figures in Table 3, it is obvious that the model-independent evaluation reveals almost the

TABLE 3. Pharmacokinetic characteristics of gentamicin

	Model-independent evaluation[1]		Model-dependent evaluation[2]
CL_{ren} [l/h]	2.97		2.64
$t_{1/2,z}$[h]	77.8 (from urine)		53.3 (from serum)
MT_{ev}[h]	22.7 (from urine)	MT_{ss}[h]	21.5 (from serum)
V_{ev}[l]	67.4	V_{ss}[l]	56.8

[1] von Hattingberg and Brockmeier (1980) using data from Wahlig *et al.*, (1975)
[2] Schentag *et al.* (1977)

same characteristics and the existence of a deep compartment, although a less sensitive analytical method was used by Wahlig and coworkers.

This result also demonstrates that the mean residence time can be derived easily from urinary data, which had been stated before by von Hattingberg on purely theoretical considerations (15).

The next example considers the different stages involved in drug absorption. However, the field of *in vitro/in vivo* correlation of dissolution will not be addressed, although we have new and provocative results (10), since this topic has already been extensively discussed by Professor von Hattingberg and Dr. Voegele at these meetings in the past.

Hammarlund and coworkers studied the total mean time for different modes of intravenous and oral administration of 40 mg furosemide in 8 subjects (16). Their results are summarized in Table 4.

TABLE 4. Mean time characteristics for intravenously and orally administered furosemide

		Mean	SEM	Range
MT_{ss}	[min]	51.4	1.5	45-60
$MT_{abs,tabl.}$ (postprandial)	[min]	144	3.9	126-158
$MT_{abs,tabl.}$ (fasting)	[min]	83.9	8.4	61-124
$MT_{gast.empt.}$	[min]	60.6	11	9-90
$MT_{abs,sol.}$ (postprandial)	[min]	109	7.3	70-131
$MT_{diss,vivo}$ (postprandial)	[min]	35.2	8.7	9-87

Data taken from Hammarlund *et al.* (16).

The mean time in the steady state volume of distribution is extremely consistent for all subjects (Table 4). The same is true for total clearance. The additivity of mean times attributed to the different steps in absorption is used to decompose the total mean time. The additivity is one of the most useful properties in the mean time analysis technique (11). For example, one can immediately read from the data that the absorption $MT_{abs.}$ is the rate-limiting step within the overall kinetic, regardless of whether this step can be modelled by a first order process or not. The mean gastric emptying time $MT_{gast.empt.}$ and its range is in good agreement with the values reported when large-scale methods, such as scintigraphy, were used.

Unfortunately, Hammarlund and coworkers did not calculate the mean time characteristics from the urinary data which they monitored. From the graphs for cumulative urinary excretion depicted it is most likely that the same results would have been obtained.

They obtained the mean *in vivo* dissolution time $TM_{diss.vivo}$ under postprandial administration as the difference between the mean absorption time for the tablet $MT_{abs.tabl.}$ and the solution $MT_{abs.sol.}$ (Table 4). However, the mean *in vivo* dissolution times cover a tenfold range which is very unlikely to be due to the formulation properties of the tablet.

Figure 2 shows the pH-dependent solubility of furosemide, and also piretanide, which rises from 20 µg/ml at pH 1-2 to 50 mg/ml at pH 7.4 (17) - more than one thousand-fold higher.

It is therefore most likely that differences in gastric pH are responsible for marked interindividual differences in solubility, and this is in fact the reason for the large variation in the mean *in vivo* dissolution times reported by Hammarlund, who gave the 40 mg tablet together with 200 ml of water or orange juice.

However, this solubility problem cannot explain the considerably large interindividual differences in the absolute bioavailability of furosemide ranging from 26 to 81 % in the study of Hammarlund *et al.* which confirms the results of earlier studies (18).

This example was chosen to demonstrate that the path of the drug through the body and its fate can be decomposed easily by the model-independent approach.

The answers may not be as complete as desirable; however, critically reviewed, they will provoke hypotheses for carefully directed investigations.

For example, we studied the absorption of piretanide after endoscopic placement of the drug at three different sites of the gastrointestinal tract under visual control (19). The median concentration profiles after instilling

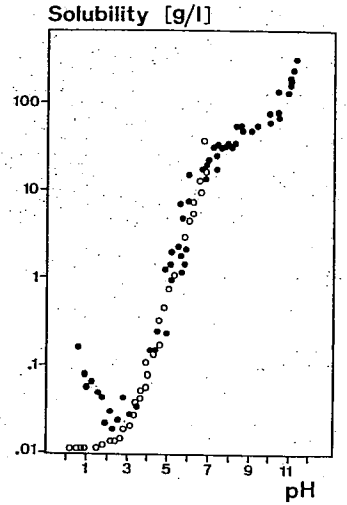


FIG. 2. pH-dependent solubility of furosemide (o) piretanide (•).

the drug into the stomach, duodenum and colon are shown in Figure 3.

It is immediately striking that the rate of absorption for the large intestine is very low. Biometricians have, however, successfully weaned clinicians off reading something directly from a graph, and have persuaded them that proving the hypothesis by adequate statistical testing is what is needed. The area under the data completed by extrapolation AUDC is depicted in Figure 4.

Datapoints connected by a line refer to the same subject. Obviously, the difference in the area under the curve for administration in the stomach and in the colon is significant. The same holds for the duodenum and colon. The difference between the stomach and duodenum is not significant.

Since the total clearance of piretanide shows small interindividual variations, as is also the case for furosemide, the area values largely reflect the amount absorbed.

Due to the slow absorption from the large intestine, the total mean time MT for this site of administration is significantly greater than for the two other sites which are not significantly different (Fig. 5).

This conclusion is possible, since the interindividual variation of the mean time for piretanide after intravenous administration is also remarkably small. This means that differences in total mean time mainly reflect differences in the mean absorption time.

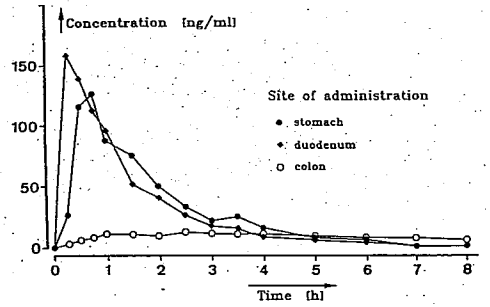


FIG. 3. Median serum concentration of piretanide after placement of the dose at three different sites of administration. The solution was instilled into the stomach (●), duodenum (▲), and ascending colon (O) under endoscopic control. (Reproduced from Brockmeier *et al.* (19) with kind permission of Springer Verlag, Heidelberg.)

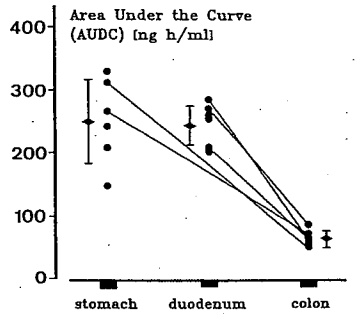


FIG. 4. The amount absorbed was measured by the area under the data completed by extrapolation (AUDC, ordinate) after placement of piretanide at different sites of the gastrointestinal tract (abscissa).

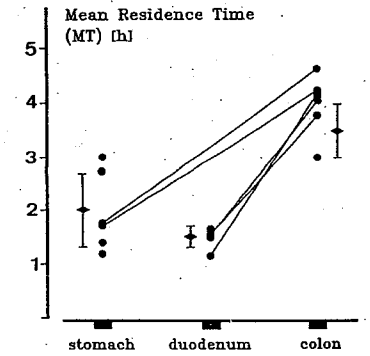


FIG. 5. Differences in the rate of absorption were measured by the total mean time (MT, ordinate).

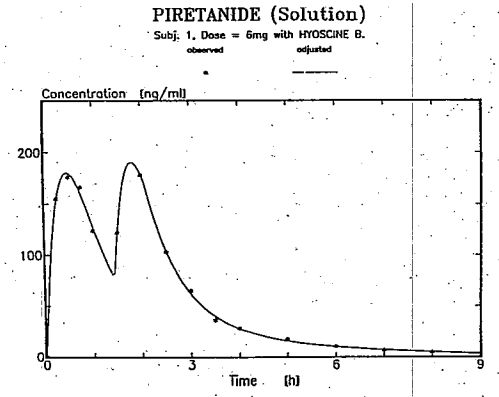


FIG. 6. Serum concentrations of piretanide after instilling a piretanide solution into the stomach (*). Before administration the stomach was immobilised with intravenous hyoscine-N-butylbromide. The solid line represents the adjusted pharmacokinetic model which states three sites of absorption with different absorption rates.

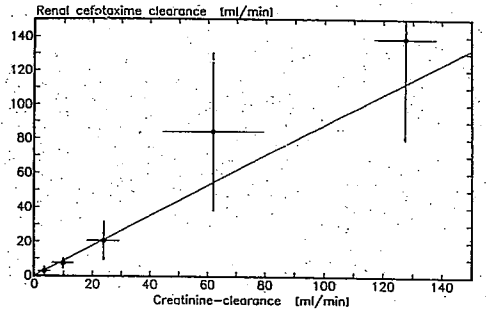
With this answer to the absorption features of the gastrointestinal tract, one may proceed to more rigorous modelling, the outcome of which is depicted in Figure 6.

The model states three sites with different absorption rates: absorption from the stomach where dissolution is certainly the rate-limiting step under unfavourable conditions, absorption from the upper intestine with a high absorption rate and from the lower intestine with a slow rate. It is important to note that the stomach was immobilised by intravenous administration of 40 mg hyoscine-N-butylbromide, and therefore the first peak *must* reflect absorption from the stomach.

A routine step in drug development is to characterize the pharmacokinetics in subjects with varying degrees of renal function. Here typical data taken from Matzke and coworkers are presented (20). They studied the disposition of cefotaxime in a group of subjects with normal creatinine clearance, mild, moderate and severe renal insufficiency and a group with endstage renal disease requiring maintenance haemodialysis. Total and renal clearance, mean residence time, and total volume of distribution were evaluated as mentioned above.

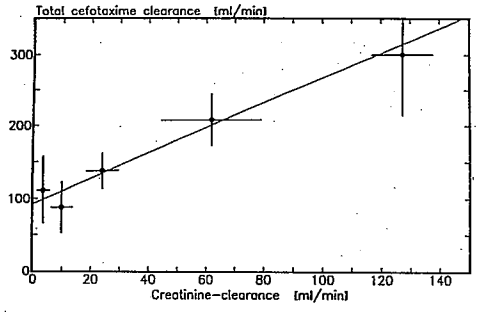
As expected, the renal clearance of cefotaxime correlates closely with the creatinine clearance. Figure 7 depicts the mean values for each of the five groups, since individual values were not reported.

The total clearance also shows a clear dependency on creatinine clearance (Fig. 8).The intercept may also



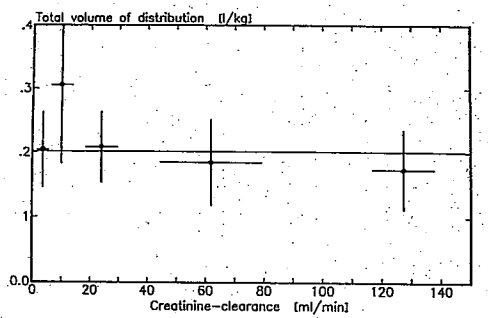
Plotted from data of Matzke et al. (1985)

FIG. 7. Renal clearance of cefotaxime. Mean values and standard deviations for five groups of patients with renal impairment characterized by their mean creatinine clearance (abscissa). Data taken from Matzke *et al.* (20).



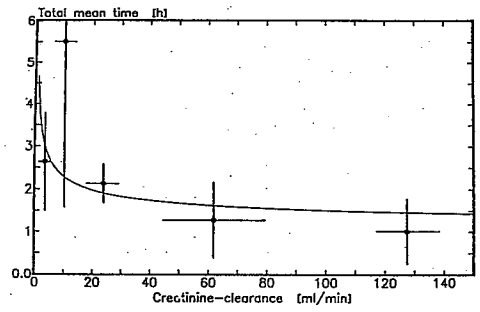
Plotted from data of Matzke et al. (1985)

FIG. 8. Total clearance of cefotaxime. Mean values are plotted versus mean creatinine clearance.



Plotted from data of Matzke et al. (1985)

FIG. 9. Total volume of distribution for cefotaxime. The mean values for five groups of patients are plotted over their mean creatinine clearance.



Plotted from data of Matzke et al. (1985)

FIG. 10. Mean residence time for cefotaxime. Mean values for five groups of patients with impairment are plotted over the respective means for creatinine clearance.

be considered as an estimate of the nonrenal clearance of cefotaxime as an average value, provided that nonrenal clearance is not affected by renal insufficiency. This concept has been proposed by Dettli (7).

The steady state volume of distribution depicted in Figure 9 shows no statistically significant dependency on creatinine clearance. Nevertheless, the question arises whether the increase in the volume of distribution below a creatinine clearance of 20 ml/min reflects the water retention in these patients.

The theoretical hyperbolic relation between creatinine clearance and mean residence time is also not very convincing, since the dialysed group shows on average a smaller mean time than the group with severe renal insufficiency (Fig. 10). Indeed, very frequently more questions arise from a study than one initially sets out to investigate.

Lalonde and his colleagues (21) administered 10 μg/kg digoxin intravenously over 5 min to 11 healthy subjects during one phase of their study; in the other phase the drug was administered together with oral ingestion of 25 g activated charcoal approximately every 4 hours. They estimated total clearance, mean residence time and steady state volume of distribution as described above. Figure 11 shows the total clearance values for both phases of the trial. It is immediately striking

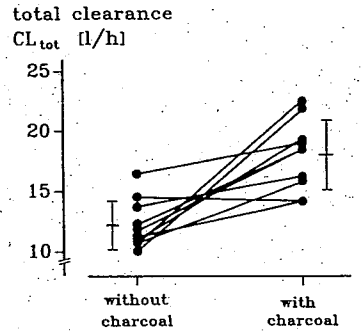


FIG. 11. Total clearance of intravenously administered digoxin with or without oral activated charcoal. Points connected by a line refer to the same subject. Data taken from Lalonde et al. (21).

that the oral administration of activated charcoal raises the total clearance clearly in all subjects but one with an average increase of 50%.

In the same manner the total mean time is reduced for all subjects but one (Fig. 12). The average decrease was also 50%, while the terminal half-lives decreased by approximately 40% on average.

An unexpected decrease in the steady state volume of distribution of about 24% was observed during the charcoal phase.

Without doubt, the main question of the trial, *i.e.* whether the total clearance of digoxin could be increas-

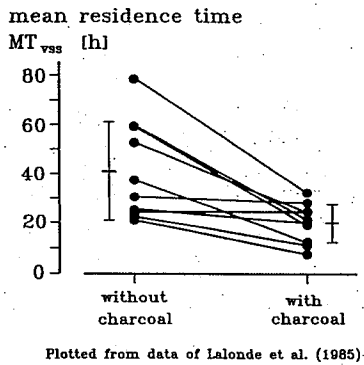


FIG. 12. Mean residence time of digoxin after intravenous administration with or without oral activated charcoal. Connected points refer to the same subject.

ed, or in other words, the mean residence time of drug in the body would be reduced by oral administration of activited charcoal, was answered clearly and quantified by model-independent evaluation.

The mechanisms for the reported effect are not clear and cannot be answered due to the design of the experiment. As discussed by the authors, enterohepatic recirculation of the drug does not seem to be essential for this effect since clearance of phenobarbital is also increased by orally administed charcoal, although phenobarbital is not known to undergo enterohepatic recirculation.

Passive diffusion of the drug from the circulation into the gastrointestinal lumen and adsorption to charcoal is discussed by the authors. It seems worth recalling that it was this rediffusion of several acidic and basic drugs into the stomach which led Shore, Brodie and Hogben to set up the pH partition hypothesis (22).

The idea of going even further in modelling the mechanisms explicitly is attractive, but this requires a more elaborate experimental setting. Nevertheless, specific pharmacokinetic trials in *healthy* volunteers cannot answer the question of which of the reported effects is of significance in the case of digoxin intoxication. This latter question must be substantiated in *patients* - especially for those with renal impairment.

In a recent publication we proposed a method of estimating the first-pass effect from a *single oral* administration using the additivity of mean times (23). The method requires the analysis of the parent drug and the metabolite and the evaluation of their mean times.

When a first-pass metabolism of relevant extent is present, the total mean time of the metabolite is the weighted sum of the mean times of the two subfractions, the one which undergoes first-pass metabolization and the one which does not:

$$\begin{aligned} MT_{sys,met} &= f\cdot(MT_{abs,orig} + MT_{vss,orig} + MT_{vss,met}) \\ &\quad + (1-f)\cdot(MT_{sys,orig} + MT_{vss,met}) \\ &= f\cdot MT_{sys,orig} + (1)\cdot MT_{abs,orig} + \\ &\quad MT_{vss,met} \end{aligned}$$

Eq. 9

The rearranged equation suggests plotting the mean time of the metabolite versus the mean time of the parent drug, and reading the fraction f - this is the availability after absorption - off the slope of the regression line.

For example, plotting the mean times of SIN1, a metabolite of molsidomine, versus the mean times of molsidomine itself evaluated for 11 healthy volunteers, yields a significant dependency with a slope of .71, which is unfortunately not significantly different from one (Fig. 13). The bioavailability estimated by area comparison for the same subjects gives a value of 55%.

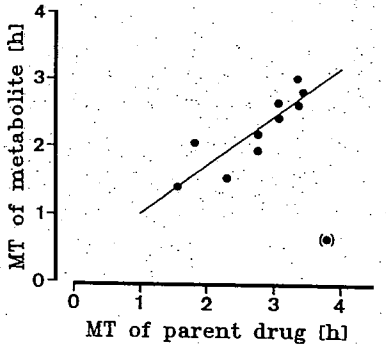


FIG. 13. The total mean time of SIN1, a metabolite of molsidomine is plotted against the total time of molsidomine itself (•). The average first-pass effect can be estimated from the regression line. (Reproduced from Brockmeier *et al.* (23) with kind permission of Springer Verlag, Heidelberg.)

The second example was taken from the literature (24) showing the total mean time for 10-hydroxy-nortriptyline versus the total mean time for nortriptyline itself (Fig. 14). The regression is significant and

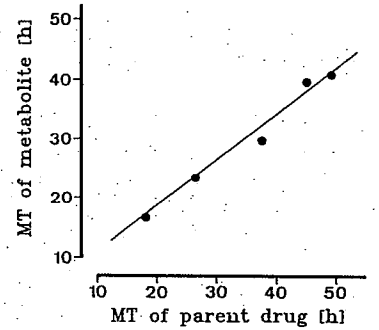


FIG. 14. The total mean time of 10-hydroxy nortriptyline versus the total mean time of nortriptyline (•). The slope of the regression line provides an estimate of the average first-pass effect. (Reproduced from Brockmeier *et al.* (23) with kind permission of Springer Verlag, Heidelberg.)

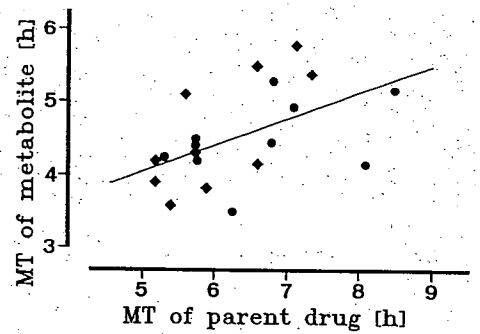


FIG. 15. The total mean time of propranolol glucuronide is plotted against that of unconjugated propranolol. Two different, bioequivalent tablet formulations of propranolol were administered (•,▲). (Reproduced from Brockmeier *et al.* (23) with kind permission of Springer Verlag, Heidelberg.)

the slope differs significantly from unity. Here again the availability after absorption estimated by the mean time method is larger than the bioavailablity calculated from area comparison, namely 76 versus 60%.

In the last example, propranolol glucuronide is plotted over the mean time of propranolol itself (Fig. 15). Due to the large scatter in the data, we used the results for both formulations compared in a bioequivalence study (25). Despite the large scatter, the regression is significant and the slope indicates a first-pass effect of 64% or an availability after absorption of 36%. The average bioavailability of propranolol has been reported as 25%.

For each of the three drugs studied, the estimated first-pass effect was smaller than would be concluded from comparison of the areas. The small number of studies analysed does not make it possible to conclude whether this indicates that the mean time method is more precise than area comparison. The theoretical advantage of the mean time method over evaluation of the first-pass effect by comparing the quotient of areas after oral and i.v. administration is clear: only the amount of drug which has actually been absorbed is accounted for, while the comparison of areas will also encompass the unabsorbed fraction, a loss which is not due to first-pass metabolism.

CONCLUSION

In general, model-independent evaluation techniques provide the answer to questions posed in a clinical trial.

This has been demonstrated by the applications referred to in this paper which dealt with completely different topics of clinical pharmacology and which is also underlined by the increasing number of publications using this technique.

However, one should not have any hesitation in proceeding to more sophisticated evaluation techniques if necessary, or if a more comprehensive answer can be obtained by using different evaluation routines.

Nevertheless, when the part of the puzzle made up by pharmacokinetics has been properly filled by quantifying characteristics, one is left with the duty of interpreting the results, which, without doubt, is sometimes the most critical part of the job.

ACKNOWLEDGEMENTS

The author is grateful to Mr. A. Reeves for his helpful suggestions about the manuscript and to Miss K. Herrnkind for her secretarial assistance.

REFERENCES

1. Himmelstein, K.J. et al. *A review of the applications of physiologically based pharmacokinetic modelling.* J Pharm Biopharm 1979; 7(2): 127-144.
2. Dost, F.H. *Ueber ein einfaches statistisches Dosis-Umsatz-Gesetz.* Klin Wschr 1958; 36: 655-657.
3. van der Waerden, B.L. Mathematical Statistics. Springer Verlag: Berlin-Heidelberg-New York 1969.
4. Brockmeier, D. et al. *Mean residence time.* Meth and Find Exptl Clin Pharmacol (accepted).
5. von Hattingberg, H.M. *Moment analysis in vivo and in vitro.* Meth and Find Exptl Clin Pharmacol 1984; 6: 589-595.
6. Brockmeier, D. *Die Rekonstruktion der Freisetzungsprofile mikroverkapselter Arzneiformen durch den Mittelwert und die Varianz der Freisetzung.* Arzneim-Forsch/Drug-Res 1981; 31(III), 10: 1746-1751.
7. Dettli, L. *Pharmakokinetische Parameter in der aerztlichen Praxis.* In: Biopharmazie. Theorie und Praxis der Pharmakokinetik. J. Meier, H. Rettig and H. Hess (Eds.). Georg Thieme Verlag 1981.
8. Brockmeier, D. *Die Bedeutung statistischer Momente der Verweildauer für die Pharmakokinetik und Biopharmazie.* Thesis, Giessen 1982.
9. Nüesch, E.A. *Noncompartmental approach in pharmacokinetics using momenits.* Drug Metabolism 1984; 15(1&2): 103-131.
10. Brockmeier, D. et al. *In vitro-in vivo correlation of dissolution, a time scaling problem? Transformation of in vitro results to in vivo situation, using theophylline as a practical example.* Eur J Clin Pharmacol 1985; 28: 291-300.
11. von Hattingberg, H.M. et al. *A method for in vivo-in vitro correlation using the additivity of mean times in biopharmaceutical models.* In: Methods in Clinical Pharmacology. N. Rietbrock, et al. (Eds.) Friedr. Vieweg & Sohn Verlag 1979.
12. von Hattingberg, H.M. et al. *The pharmacokinetic basis of optimal antibiotic dosage.* Infection 1980; 8: 21-24.
13. Wahlig, H. et al. *Ergänzende Untersuchungen zur Pharmacokinetik von Gentamicin.* Infection 1975; 3: 217-222.
14. Schentag, J.J. et al. *Gentamicin disposition and tissue accumulation on multiple dosing.* J Pharmacokin Biopharm 1977; 5,6: 559-577.
15. von Hattingberg, H.M. et al. *A concept for the assessment of bioavailability in complex systems in terms of amounts and rates.* In: G. Bozler and J.M. van Rossum (Eds.) Pharmacokinetics During Drug Developmet. Gustav Fischer Verlag: Stuttgart/New York 1982.
16. Hammarlund, M.M. et al. *Pharmacokinetics of furosemide in man after intravenous and oral administration. Application of moment analysis.* Eur J Clin Pharmacol 1984; 26: 197-207.
17. Sistovaris, N. et al. Piretanide - *Investigation of physicochemical properties.* Internal Report, Hoechst AG 1978.
18. Benet, L.Z. *Pharmacokinetics/pharmacodynamics of furosemide in man: A review.* J Pharmacokin Biopharm 1979; 7, 1: 1-27.
19. Brockmeier, D. et al. *The absorption of piretanide from the gastro-intestinal tract is site-dependent.* Eur J Clin Pharmacol 1986; 30: 79-82.
20. Matzke, G.R. et al. *Cefotaxime and desacetyl cefotaxime kinetics in renal impairment.* Clin Pharmacol Ther 1985; 38,1: 31-36.
21. Lalonde, R.L. et al. *Acceleration of digoxin clearance by activated charcoal.* Clin Pharmacol Ther 1985; 37,4: 367-371.
22. Shore, P.A. et al. *The gastric secretion of drugs: A pH partition hypothesis.* J Pharmacol Exp Ther 1957; 119: 361-369.
23. Brockmeier, D. et al. *Mean time and first-pass metabolism.* Eur J Clin Pharmacol 1985; 29: 45-49.
24. Alvan, G. et al. *First pass hydroxylation of nortriptyline: Concentrations of parent drug and major metabolites in plasma.* Eur J Clin Pharmacol 1977; 11: 219-224.
25. Midha, K.K. et al. *Pharmacokinetics of glucuronidation of propranolol following oral administration in humans.* Biopharm Drug Dispos 1983; 4: 331-338.

Send reprint requests to: Dr. D. Brockmeier, Hoechst AG, Klinische Forschung, H840, 6230 Frankfurt/M-80, FRG