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THE ROLE OF PHARMACOKINETICS IN DRUG PRODUCT DESIGN *

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INTRODUCTION

The pharmacokinetics and pharmacodynamics of today's new chemical entities are studied in much more detail than the compounds of a few years ago. This adds greatly to the complexity of the development program, but the outcome is a drug product with maximum benefit to the patient.

Attempts at the quantitative description of drug elimination were reported in the literature as early as the 1920s (Widmark, 1919; Widmark and Tandberg, 1924). Pharmacokinetics, as we know it today, and the recognition of its importance in medicine did not surface until the early 1950s. Prior to 1950 the most notable effort was that of Teorell (1937a and b) whose concept of compartments paved the way for subsequent research. The term 'pharmacokinetics' was first used by Dost (1953).

In the quarter of a century since those early beginnings, progress has been made. It is now generally appreciated that a basic understanding of the pharmacokinetics of a drug substance leads to improved therapy. This was dramatically demonstrated by the early work of Kruger-Thiemer with sulfa drugs. He showed how knowledge concerning the pharmacokinetics and the solubility of sulfa drugs and their acetylated metabolites could be used together to predict the risk of crystalluria and, thus, to provide a means to optimize dosage regimens (Kauger-Thiemer and Bunger, 1965). This work was certainly classical and established the utility of pharmacokinetics as an invaluable tool in therapeutics. However, it is safe to say that we have barely scratched the surface in applying this tool to its full potential.

The currently popular, often maligned, concept of bioavailability evolved from concerns for the inconsistent performance among orally administered vitamin preparations (Oser et al., 1945). Its working definition as the rate and the amount of the administered drug which reaches the general circulation intact (Riegelman et al., 1973) has sufficed if one is interested only in drug absorption but is limiting with regard to the end result. The intensity and duration of the therapeutic and/or toxic effect of the drug are determined

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by the time course of change in concentration at the receptor site. This expanded concept of bioavailability, receptor site availability, if you will, and the interrelationship of pharmacokinetics and pharmacodynamics has been simply and eloquently expressed by Dettli and Spring (1968). Namely, the kinetics of drug absorption, distribution, and elimination determines the concentration of the active species at the target organ, the quantitative values of which determine the intensity and duration of the pharmacological effect. Thus, there is a mutual interdependence between the effect of the organism on the drug (pharmacokinetics) and the effect of the drug on the organism (pharmacodynamics).

The pharmacological agents coming out of research programs today will require more precise dosing than those of the past. These agents are more specific in their action, in many cases being targeted to a specific tissue or enzyme system. These substances will require careful pharmacokinetic characterization which is essential to the design of the dosage form and of the dosage regimen. Greater emphasis will be placed upon the needs of the individual patient. The practicing physican and pharmacist must receive data in a form which they can readily apply in the clinical setting to ensure that the individual patient is being optimally treated. Advances in analytical techniques have greatly facilitated the determination of minute quantities of drug and metabolites in body fluids, thus enabling the elucidation of metabolic pathways at an early phase of drug product development. Similar advances in the techniques of clinical, pharmacokinetic, and statistical evaluation will be needed to meet the challenges of tomorrow. To quote Homer Smith (1962), '. . . the ever-widening horizons and increasing details of medicine make the art of healing more difficult and yet more certain'.

In this paper, an attempt will be made to present some basic principles of pharmacokinetics with simple illustrations of their application in the design and evaluation of drug products.

PHARMACOKINETIC REVIEW

A fundamental principle in pharmacokinetic analysis is to achieve material balance at all times. Eqn. 1 states that the amount eliminated after a single dose equals the amount absorbed, i.e.:

$$FD = \dot{V}_p A^1_\infty \tag{1}$$

where F is the fraction absorbed (bioavailability), D is the dose, $\dot{V}_p$ is the plasma clearance, and A^1_∞ is the total area under the plasma concentration curve. Most situations encountered in drug product design and evaluation can be accommodated by appropriate substitution in and/or rearrangement of Eqn. 1.

In bioavailability assessment, for example, Eqn. 1 is rearranged such that

$$F = \frac{\dot{V}_p A^1_\infty}{D} \tag{2}$$

Since the dose is known and A^1_∞ can be estimated from the plsma concentration profile, only $\dot{V}_p$ on the right-hand side of Eqn. 2 remains to be determined. The plasma clearance

in a given subject can be measured independently following an intravenous dose, which is given either in a separate experiment or concurrently using labelled drug. In either case, since F is by definition 1.0 after an i.v. dose,

$$\dot{V}_p = \left(\frac{D}{A^1_\infty}\right)_{iv} \tag{3}$$

When the isotope method is used, $(A^1_\infty)_{iv}$ is determined by the time course of change of the label identified specifically with the unchanged drug. The label may be a stable isotope or a radioactive one, the quantitation of which is effected either by GC/MS techniques or by radiometric methods.

Fig. 1 is a simulation of the change in plasma concentration on chronic administration of the same dose, D, at repeating dosing intervals τ. Drug accumulates at an ever-decreasing rate to a steady-state. The time averaged plasma concentration at steady state, $\bar{C}^{ss}_p$, is represented by the dotted horizontal line.

Area under the plasma concentration curve over interval τ at steady-state, A^{ss}_τ or $\tau\bar{C}^{ss}_p$, is equal to A^1_∞ (Wagner et al., 1965). Equality among the shaded areas in Fig. 1 is a visual confirmation. Substituting for A^1_∞ in Eqn. 1,

$$FD = \dot{V}_p A^{ss}_\tau = \dot{V}_p \bar{C}^{ss}_p \tau \tag{4}$$

At steady-state, therefore, the amount absorbed equals the amount eliminated, which is as it should be.

The effect of dose and dosage regimen can be studied with the aid of Eqn. 4. First, the mean plasma level to be achieved on chronic treatment by a given dosage regimen is

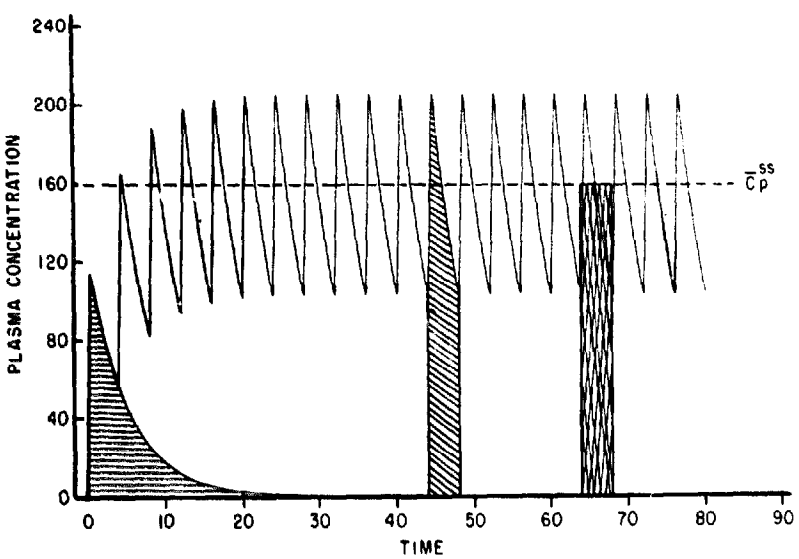

Fig. 1. Simulated time course of drug accumulation on chronic administration. Shaded areas are equal in magnitude.

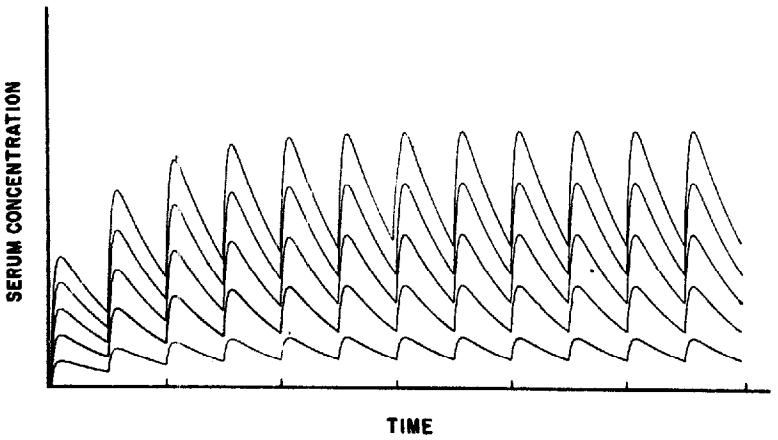

Fig. 2. Steady-state serum concentrations increase in proportion to the dose administered at a given frequency.

determined by

$$\bar{C}_p^{ss} = \frac{FD}{\tau \dot{V}_p} \tag{5}$$

Eqn. 5 also states that the mean plasma level at steady-state is directly proportional to the dose (Fig. 2) and inversely proportional to the dosage interval (Fig. 3).

Second, if the desired therapeutic plasma level were $\bar{C}_p^{ss}$, the appropriate dosage regimen would be

$$\frac{D}{\tau} = \frac{\dot{V}_p \bar{C}_p^{ss}}{F} \tag{6}$$

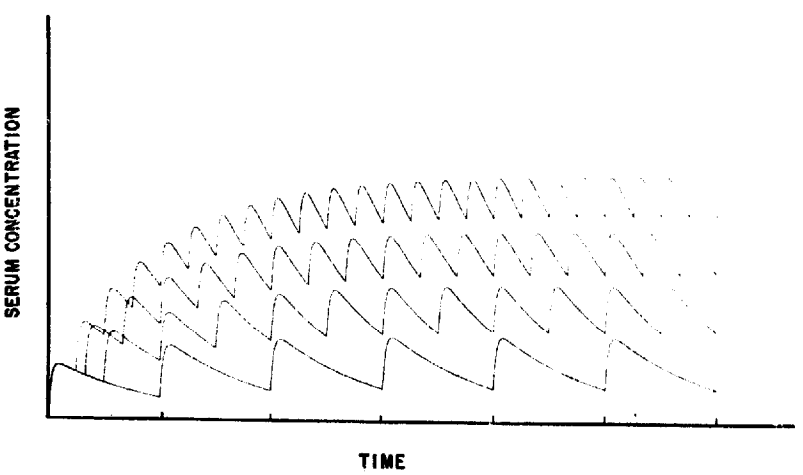

Fig. 3. Steady-state serum concentrations increase in proportion to dosing frequency.

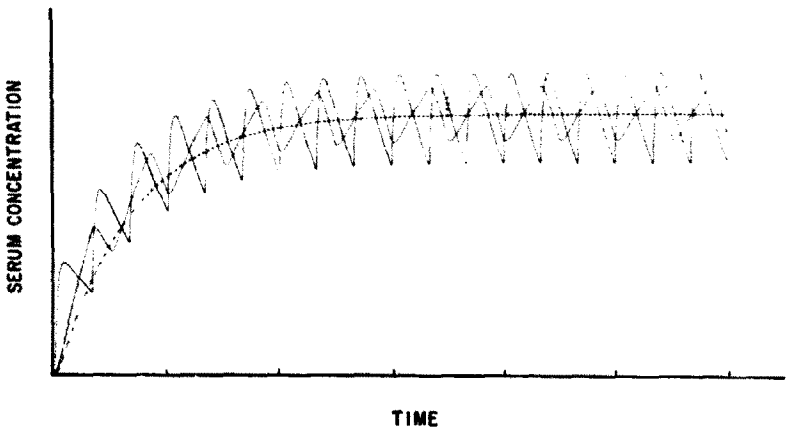

Fig. 4. At a given daily dose, the same mean steady-state concentration is achieved regardless of the dosing regimen; viz., every 8 h, every 12 h, or constant infusion.

Obviously, Eqn. 6 can be satisfied by giving small doses frequently or larger doses less frequently (Fig. 4).

Finally, it is evident from Figs. 1–4 that it takes time to reach a steady-state. There are situations in which it is highly desirable that therapeutic levels should be achieved as soon as possible. This can be accomplished by an initial loading dose which is larger than the maintenance dose given subsequently. The size of such a loading dose, D_1, that would permit $\bar{C}_p^{ss}$ to be attained immediately can be calculated by

$$D_1 = \frac{\dot{V}_p \bar{C}_p^{ss}}{F} \tag{7}$$

The observed plasma profile following a given dose or dosage regimen is a function of the plasma clearance and the terminal half-life, $t_{1/2}$. Whereas $\dot{V}_p$ is a determinant of the ultimate levels to be attained at steady-state ($\bar{C}_p^{ss}$), $t_{1/2}$ determines the rate of attainment. Whereas plasma clearance is solely influenced by the rate of drug elimination, the plasma $t_{1/2}$ can be affected by other factors of drug disposition such as distribution and absorption rate. In the design of drug products and of dosage regimens, $\dot{V}_p$ and $t_{1/2}$ can be manipulated independently.

Plasma clearance can be resolved into component parts of drug elimination such that

$$\dot{V}_p = \dot{V}_r + \dot{V}_m + \dot{V}_b + \ldots \tag{8}$$

where $\dot{V}_r$, $\dot{V}_m$, and $\dot{V}_b$ are respectively the renal, metabolic, and biliary clearances, whose individual products with A_∞^1 are estimates of the amount of drug excreted in urine, by metabolic transformation, and in bile. The relationship between plasma clearance and half-life is given by Eqn. 9.

$$\dot{V}_p = \frac{V_o \ln 2}{t_{1/2}} \tag{9}$$

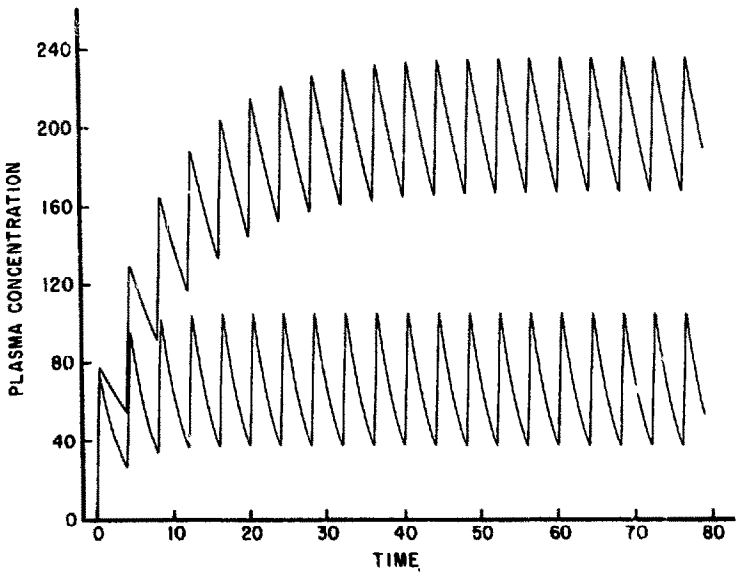

Fig. 5. Effect of plasma half-life on the rate and extent of drug accumulation; $t_{1/2}$ of upper curve is 3 times longer than that of the lower curve.

where V_o is a volume of distribution, which can be looked upon simply as a proportionality constant having dimensions of volume. Combining Eqns. 4 and 9,

$$\bar{C}_p^{ss} = \frac{F}{V_o \ln 2} \cdot \frac{D}{\tau} \cdot t_{1/2} \tag{10}$$

It is apparent that $\bar{C}_p^{ss}$ is directly proportional to $t_{1/2}$ for a given regimen providing that bioavailability is constant from dose to dose. The plasma half-life also affects the rate of drug accumulation. Fig. 5 illustrates the rate and extent of accumulation of two substances whose $t_{1/2}$ differ by a factor of 3. On repeated dosing, drug accumulates to 90% of the steady-state level after about 3.3 half-lives, 99% after 6.6 X $t_{1/2}$, etc. (Van Rossum, 1968).

It is important to note that changes in plasma $t_{1/2}$ do not always signal a change in plasma clearance, but the converse is not true. Fig. 6 shows a family of simulated plasma concentration profiles with the same $\dot{V}_p$. When absorption is rapid, $t_{1/2}$ after oral dosage is identical to that following an intravenous dose. When absorption rate is progressively slowed, deviations occur until eventually the terminal slope is controlled solely by the absorption rate. However, since $\dot{V}_p$ is unaffected by absorption, the same $\bar{C}_p^{ss}$ would be obtained on chronic administration. On the other hand, the rate of accumulation to steady-state would differ. Thus, the attainment of a steady-state with a given drug would be delayed if its release from the dosage form were to become the overall rate-limiting process.

In summary, some of the basic elements in pharmacokinetics have been identified as the dose, the dosage interval, bioavailability, clearance, and half-life. Their role in drug

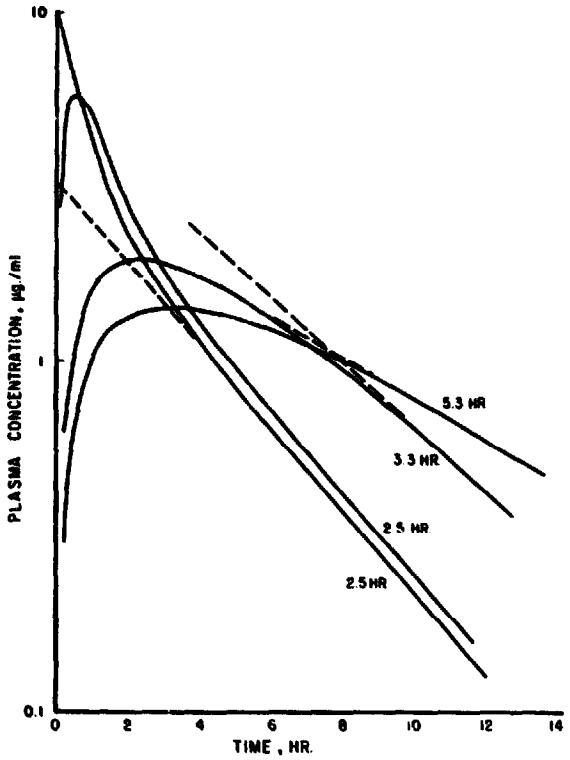

Fig. 6. Effect of absorption rate on plasma half-life; plasma clearance rate is the same in all cases.

product design and evaluation will be discussed with the aid of recent examples from our laboratories.

EXAMPLES

Halofenate

According to Eqn. 1, total area under the plasma concentration curve should be proportional to dose providing that clearance and bioavailability remain constant, i.e.,

$$A_{\infty}^{1} = \frac{F}{V_p} \cdot D \tag{11}$$

Fig. 7 shows the plasma concentration profiles of halofenate acid after oral doses of 250, 500 and 1000 mg of halofenate in healthy volunteers. Total areas were estimated by extrapolation to infinity and their relationship to dose plotted in Fig. 8. The fact that the plasma half-lives are essentially the same suggests that plasma clearance remains unchanged with dose. Constancy in bioavailability can also be inferred from Fig. 8, which shows a straight line through the origin with a slope of 1.0 as required by Eqn. 11.

Fig. 9 shows the predicted time course of accumulation in plasma after oral doses of halofenate administered by two different regimens, 1000 mg every 24 h or 500 mg every 12 h. Agreement between observed and predicted plasma levels are shown in Fig. 10.

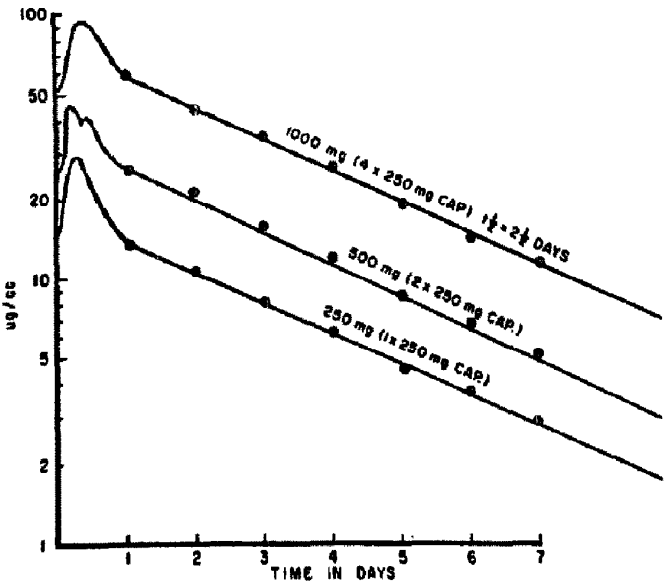

Fig. 7. Plasma concentration profiles of halofenate acid following oral administration of halofenate in man.

	Experimental Value	Theoretical Value	t Value	t .05 Tab. value for I.D.F.
Intercept	- .0475 (negative)	0	1.16	12.6
Slope	1.0386	1	.59	12.6

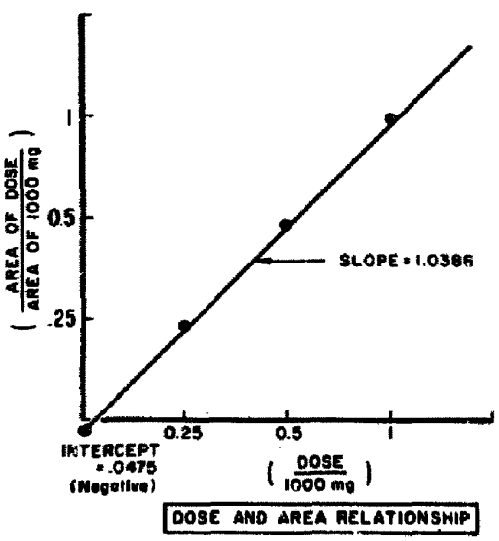

Fig. 8. Normalized area ratios of halofenate acid as a function of dose.

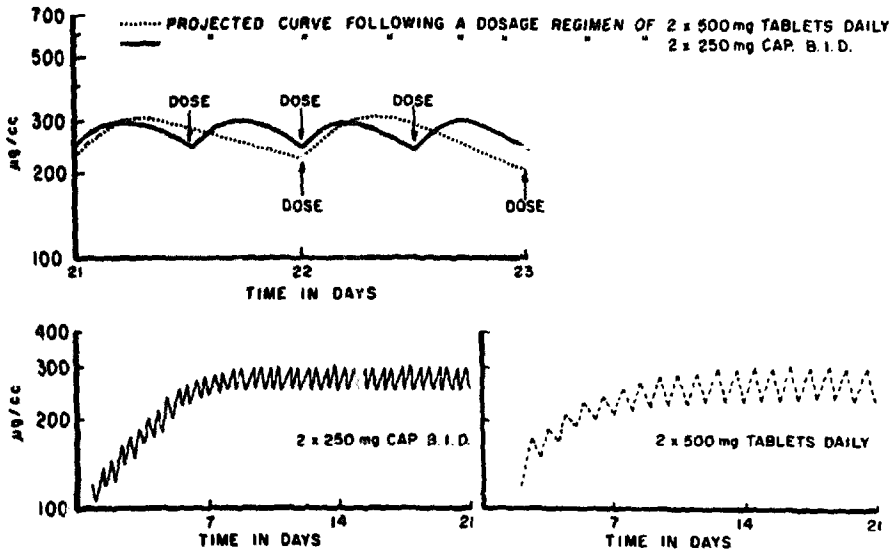

Fig. 9. Predicted time courses of accumulation of halofenate acid in plasma on chronic administration of halofenate 500 mg every 12 h or 1000 mg every 24 h.

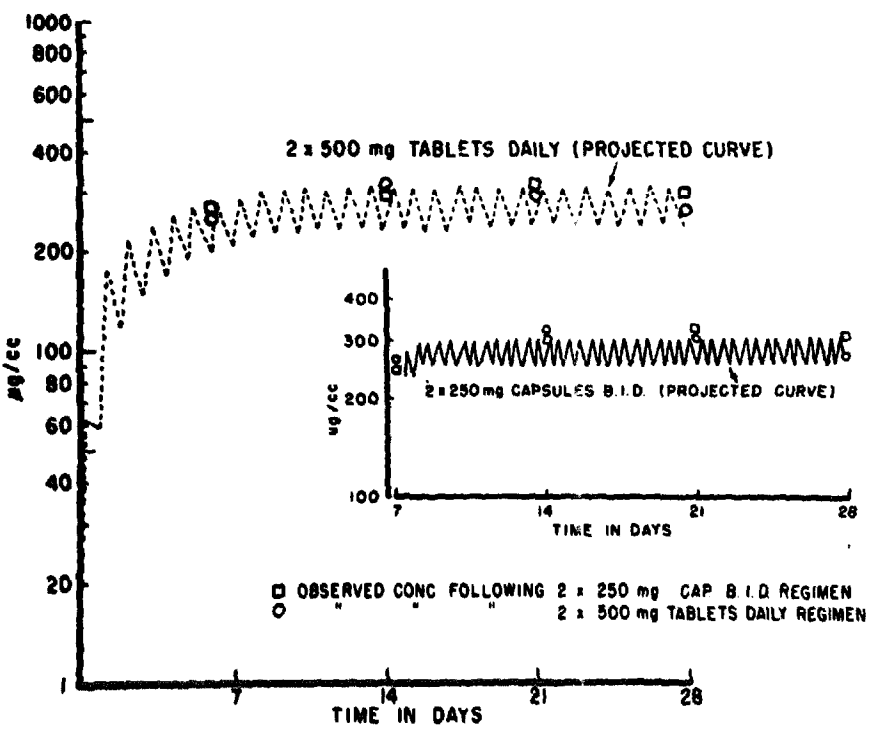

Fig. 10. Comparison between observed and predicted plasma levels of halofenate acid during chronic administration of halofenate.

Pivampicillin and ampicillin

Factors affecting bioavailability may be classified as physical, chemical, metabolic and unintentional. We shall not discuss the latter which is the source of most, if not all, of the uncertainties pertaining to therapeutic equivalence and of product interchangeability. Particle size, crystal forms, pK_a, etc. are physical characteristics which affect the chemical potential at the absorption site. Chemical modification, on the other hand, generally results in a change in drug permeability. While chemical decomposition and first-pass metabolism usually contribute negatively to bioavailability, the same properties are sometimes highly desirable such as when prodrugs or active metabolites are involved.

Orally administered ampicillin is absorbed variably and incompletely. Two crystalline forms of ampicillin are used clinically. The anhydrous form is more soluble and rapidly dissolving than the trihydrate (Poole et al., 1968). Pivampicillin is the pivaloyloxymethyl ester which hydrolyzes to ampicillin in the presence of esterases (von Daehne et al., 1970). Fig. 11 shows the serum concentrations of ampicillin following an intravenous dose of ampicillin sodium and equivalent oral doses of ampicillin anhydrous, ampicillin trihydrate, and pivampicillin HCl in 12 healthy volunteers (Loo et al., 1974). Similarities in half-life among the 4 treatments would indicate that neither absorption nor hydrolysis was rate limiting. The time course of appearance of ampicillin in the general circulation following the 3 oral treatments are shown in Fig. 12. A small, but clearly discernible, difference in bioavailability is seen between the anhydrous and the trihydrate forms. The fact that more than 80% of the administered pivampicillin is available as ampicillin and

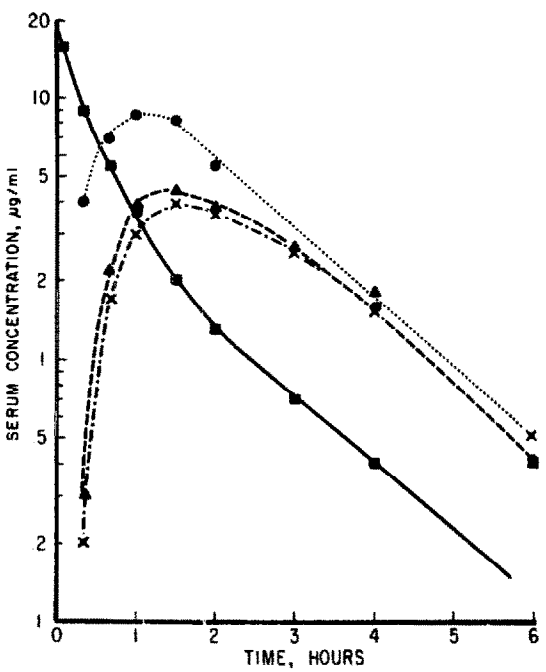

Fig. 11. Serum concentration profiles of ampicillin after an intravenous dose of ampicillin sodium (■) and oral doses of ampicillin anhydrous (▲), ampicillin trihydrate (×), and pivampicillin HCl (●).

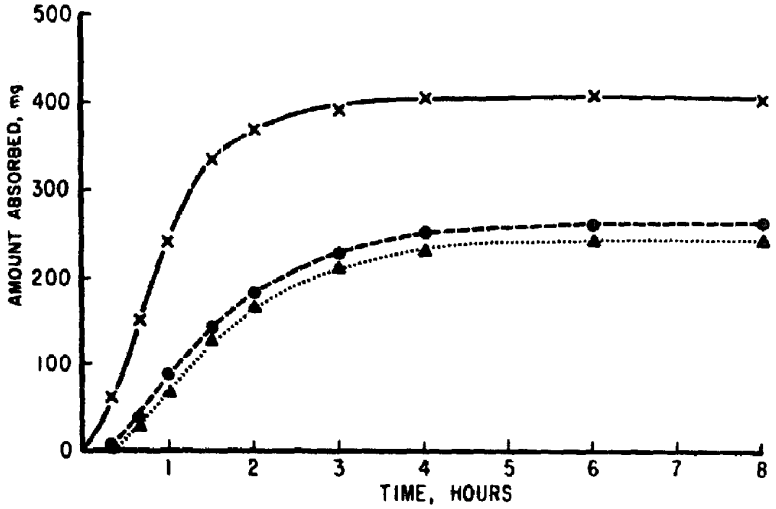

Fig. 12. Absorption profiles of ampicillin following single oral doses of amplicillin anhydrous (●), ampicillin trihydrate (▲), and pivampicillin HCl (×).

that the ensuing serum half-life is similar to those of the other treatments strongly suggests that hydrolysis occurred mainly during the first-pass through the liver and the gut wall. Direct evidence of complete hydrolysis in the gut wall was provided by Lund et al. (1976) who found only trace quantities of pivampicillin in the portal venous blood of patients during the absorption phase.

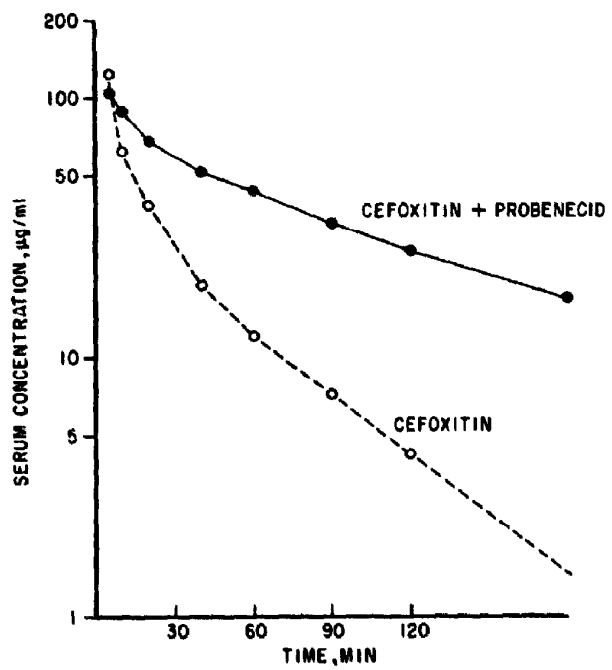

Fig. 13. Effect of probenecid on the serum concentration profile of cefoxitin in man.

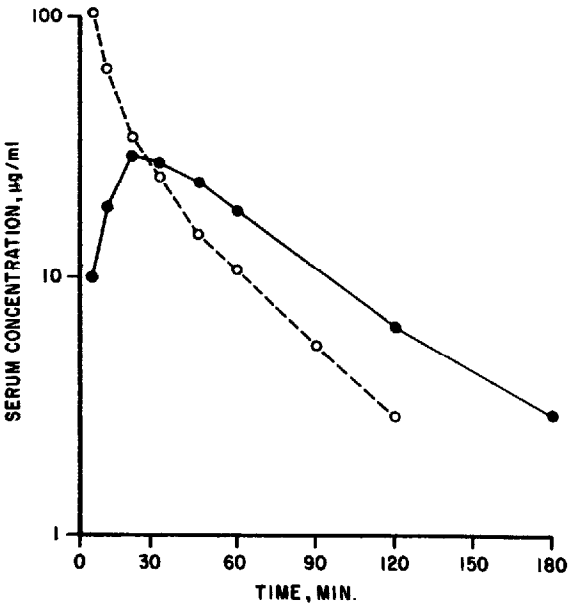

Fig. 14. Serum concentrations of cefoxitin after intravenous (○) and intramuscular (●) administration of sodium cefoxitin in man.

Cefoxitin sodium

The renal tubular secretion of many organic acids is decreased in the presence of probenecid. It is therefore often coadministered with other drugs, notably with β-lactam antibiotics to prolong effective serum concentrations. Cefoxitin is a cephamycin antibiotic with a mean renal clearance of 250 ml/min. Following a 1-gram infusion of probenecid, the mean renal clearance of cefoxitin is reduced to 100 ml/min, signifying a complete inhibition of renal tubular secretion (Goodwin et al., 1974). This effect of probenecid on cefoxitin excretion is also reflected as an increase in serum half-life from 40–80 min and a corresponding increase in area under the serum concentration curve (Fig. 13).

Intramuscularly administered cefoxitin sodium is completely but slowly absorbed (Sonneville et al., 1977). Mean serum concentration profiles after comparable i.m. and i.v. doses of cefoxitin sodium in the same healthy volunteers are shown in Fig. 14. The longer serum $t_{1/2}$ after the i.m. dose is attributed to the rate of absorption which is slower than the slowest disposition rate, manifested as the serum $t_{1/2}$ after the i.v. dose. Differences in extrarenal clearance between treatments is not an alternative explanation because similar fractions of the dose were recovered in the urine.

Levodopa and carbidopa

In the treatment of Parkinson's disease, levodopa is used as a metabolic precursor of dopamine which does not cross the blood–brain barrier. Massive oral doses are usually required because decarboxylation takes place rapidly and prematurely in the gastrointestinal lumen (Rivera-Calimlim et al., 1970), in the gut wall (Kaplan and Cotler, 1976), and in the peripheral circulation. Concomitant administration of carbidopa, a DOPA decarboxylase inhibitor, permits a significant reduction in the dosage requirement with a corre-

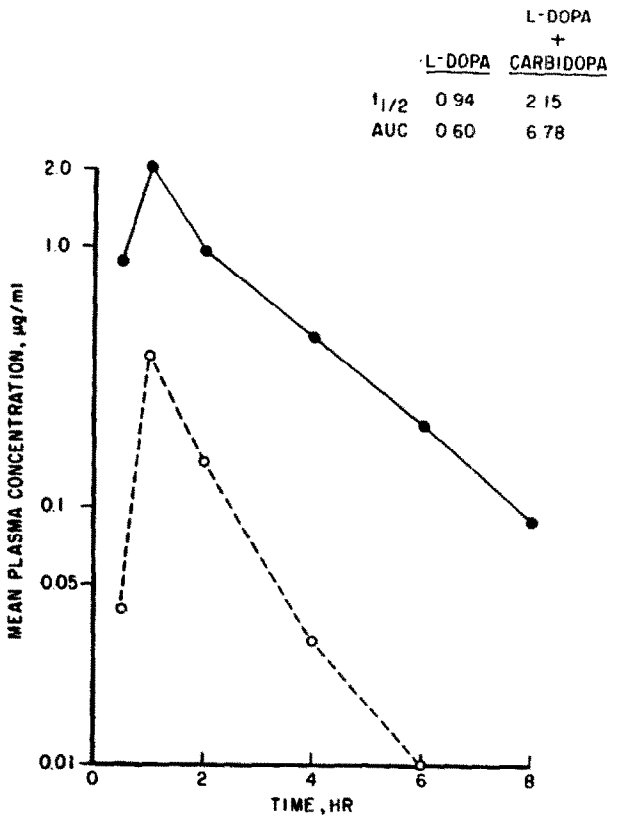

Fig. 15. Effect of concomitant carbidopa on the plasma concentration profile of levodopa in man.

sponding reduction in gastrointestinal side-effects, e.g., nausea and vomiting.

Mean plasma concentration of levodopa when administered as a single 250-mg dose alone or concomitantly with carbidopa 50 mg t.i.d. are shown in Fig. 15. In the presence of carbidopa, A^1_∞ is higher by a factor of 11 while $t_{1/2}$ is only 2.5 times longer. The difference in half-life reflects the inhibitory effect of carbidopa on the decarboxylation of levodopa after it has reached the general circulation and contributed only partially to the observed difference in the area under the plasma curve. The remaining difference in A^1_∞ is attributed to its effect on pre-systemic decarboxylation. Thus, the overall effect of concomitant carbidopa is to increase the bioavailability of orally administered levodopa and to decrease its rate of elimination after absorption. Consequently, more levodopa is available for longer periods of time for transport to the CNS, where it becomes a source of dopamine.

Sulindac

Examples cited thus far are readily amenable to straightforward pharmacokinetic treatment; more complex situations are also common. A recent example of the latter is sulindac, a new non-steroidal anti-inflammatory agent.

Fig. 16 shows the major metabolic pathways of sulindac (Hucker et al., 1973; Duggan

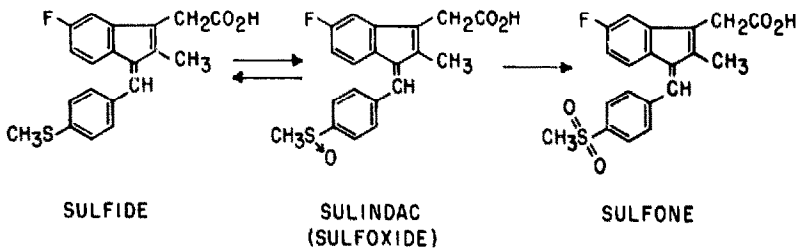

Fig. 16. Major biotransformation pathways of sulindac.

et al., 1977a). Systemically, sulindac is oxidized irreversibly to the sulfone and reduced reversibly to the sulfide. Enterically, reduction of sulindac to the sulfide is also possible, particularly under anaerobic conditions. All available evidence suggests that the pharmacological activity resides mainly, if not exclusively, with the sulfide metabolite (Duggan et al., 1977b). All 3 redox species undergo enterohepatic circulation. Because of these attributes and because there is no dosage form for intravenous use in man, direct determinations of plasma clearance, half-life, and bioavailability would not be possible. A somewhat circuitous stratagem was used. Table 1 summarizes the fecal recovery of sulindac and metabolites after oral doses of 100, 200 and 400 mg of [^{14}C]sulindac. Based on the difference between the dose and the fraction recovered in the feces as sulindac, one may conclude that absorption of sulindac is 99% complete regardless of dose. However, if enteric reduction were considered, fecal sulfide could represent unabsorbed sulindac, in which case one would estimate sulindac to be 88% absorbed. Because of enterohepatic circulation, both estimates must be considered minimal.

During repeated administration of the same dose at intervals τ, the area under the plasma concentration curve over the nth interval, A_τ^n, is related to A_τ^{ss} by Eqn. 12 (Van Rossum and Tomey, 1968).

$$A_\tau^{ss} = \frac{A_\tau^n}{1 - e^{-n\omega\tau}} \tag{12}$$

where

$$\omega = \ln 2/t_{1/2} \tag{13}$$

TABLE 1

FECAL RECOVERY OF SULINDAC AND METABOLITES AFTER ORAL DOSES OF SULINDAC IN MAN

Dose (mg)	Per cent of dose			
	Sulindac	Sulfide	Sulfone	Others

TABLE 2

MEAN AREA UNDER THE PLASMA CONCENTRATION CURVES, A_7^n, OF SULINDAC AND SULFIDE METABOLITE AFTER 200-mg DOSES OF SULINDAC

	Area ($\mu g \cdot h \cdot ml^{-1}$)		Half-life (h)
	A_{12}^1	A_{12}^{11}	
Sulindac	13.1	24.0	10.6
		17.1	5.8
		17.8	6.3
		22.0	9.2
			7.8
Sulfide	14.9	50.3	24.4
		32.4	13.5
		33.7	14.3
		35.3	15.2
			16.4

Table 2 shows the mean A_7^n of sulindac and of the sulfide metabolite for several studies in which subjects received a single 200 mg dose or 11 doses of sulindac 200 mg every 12 h. Effective half-lives of sulindac and sulfide are estimated to be 7.8 and 16.4 h, respectively, by solving Eqns. 12 and 13 where n = 1 and 11; viz.,

$$\frac{A^{11}}{A^1} = \frac{1 - e^{-11\omega\tau}}{1 - e^{-\omega\tau}} \tag{14}$$

Given an estimate of $t_{1/2}$, $\bar{C}_p^{ss}$ of sulindac for the prescribed regimen can be calculated by

TABLE 3

AREA RATIOS OF SULINDAC TO SULFIDE AFTER THE nth DOSING INTERVAL OF SULINDAC, 200 mg, EVERY 12 h

Treatment	Dosing interval	
	First	Eleventh
Tablet/fed	0.91	–
Tablet/fasting	–	0.55
Tablet/fed	0.82	–
Tablet/fasting	–	0.59
Tablet/fasting	–	0.55
Tablet/fasting	0.91	–
Solution/fasting	0.86	–
Tablet/fasting	–	0.58

Eqn. 12, i.e., A_τ^{ss}/τ. It also follows from Eqn. 5 or 6 that the mean plasma clearance of sulindac is between 165 and 186 ml/min since its bioavailability is at least 88% ($0.88 \leqslant F \leqslant 1.00$).

Finally, Table 3 shows the mean A_τ^n ratios of sulindac to sulfide for several studies in which sulindac was administered under different conditions. Their consistency for a given n would indicate that mean plasma concentration of the active sulfide can be predicted reliably from the corresponding sulindac levels (Kwan and Duggan, 1977). In short, all of the elements necessary to the design of drug product and dosage regimen have been identified and estimated.

ACKNOWLEDGEMENTS

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