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KINETICS OF PLASMA DRUG LEVELS AFTER SUSTAINED RELEASE DOSAGE

R. G. WIEGAND and J. D. TAYLOR

Chemical Pharmacology Section, Abbott Laboratories, North Chicago, Illinois

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Abstract—Equations giving plasma and urinary drug levels in terms of apparent first order absorption and elimination of drug, apparent volume of distribution of drug per kilogram, time, and release characteristics of sustained release preparations, are derived for the cases of oral administration of drug solution or a sustained release preparation. The equations are shown to describe the plasma levels obtained in dogs after administration of HT1479 (1-(*o*-methoxyphenyl)-4-(*γ*-methoxypropyl)-piperazine phosphate) as an oral solution or in sustained release tablets. The apparent first order constants for absorption and disappearance of drug from plasma were 2·0 hr^{-1} and 0·28 hr^{-1}, respectively, and the release constants for the Gradumet tablet were similar to those obtained *in vitro*.

MATHEMATICAL equations giving plasma levels of drugs after oral administration, based on first order absorption and elimination rates, have been derived by Genlen,[1] Teorell,[2] Butler, *et al.*,[3] Dost,[4] and Warter and Metais.[5] With the exception of those of Warter and Metais,[5] the equations are all of the same basic type described by Bray and White[6] for a sequence of two irreversible first order processes. There is evidence that, for some drugs, either absorption or elimination, or both, do follow apparent first order kinetics,[3, 5, 7, 8] and thus the mathematical treatment of these phenomena allow calculation of rate constants which adequately describe the system.

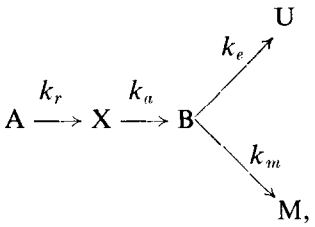
Sustained release preparations, a type of oral medication designed to liberate at least a fraction of the drug content in a continuous manner over a period of several hours, have been shown in some instances to release this drug in an exponential manner *in vitro*.[9] If the release of drug *in vivo* is also an apparent first order process, the kinetics of plasma drug levels should be described by an extension of the equation for plasma levels of drugs absorbed and eliminated by first order kinetics. This will be complicated by the release of a fraction of the dose essentially immediately, this fraction following the simpler two-sequence equation, but the complete system can be described by a single equation incorporating the parameters of release, absorption, and elimination.

A kinetic analysis of plasma drug levels is important to a clear understanding of the absorption and elimination of drugs and the effect of sustained release dosage forms. The mathematical treatment presented in this paper is straightforward and gives a sound basis on which to evaluate the effectiveness of delayed release of drug.

MATHEMATICAL DERIVATION

After administration of a sustained release preparation, it is assumed below that

drug will pass irreversibly through a series of compartments before it is eventually excreted or metabolized. The first compartment to consider is the sustained release preparation itself. From the preparation, drug is released into the gastrointestinal tract, and is then absorbed into the plasma and other tissues of the body. From the plasma the drug may be excreted into the urine or metabolized. These transformations can be shown in a flow diagram as follows:



where A indicates the sustained release preparation, X indicates the gastrointestinal tract, B the plasma and other tissues of the body, U the urine, and M the total metabolites in plasma, tissue or urine. In the derivation which follows, the amounts of drug in each compartment at any time t will be denoted by the small letters a, x, b and u for the compartments with the respective designations. Assuming that the rate of transfer from one compartment to the next is in each case proportional to the amount of drug in the preceding compartment, first order rate constants can be assigned as indicated above, k_r being the first order release constant, k_a the first order absorption constant, k_e the first order excretion constant, and k_m the first order metabolism constant.

For a sustained release preparation which releases at least a fraction of its drug content at a rate which is proportional to the amount of drug remaining in the tablet (a),

$$-\frac{da}{dt} = k_r a \tag{1}$$

expresses the rate of change of amount of drug remaining in the tablet. If the amount of drug in the tablet before administration is a_o, and the fraction f_r is released exponentially, equation (1) upon integration gives the amount of drug remaining in the tablet* at any time t as

$$a = a_o f_r e^{-k_r t} \tag{2}$$

The amount of released drug in the gastrointestinal tract at time zero for a sustained release preparation which releases a fraction (f_i) of its drug content immediately is $a_o f_i$. The amount of drug in this compartment at any time t is increased by continued release from the tablet and decreased by absorption into the plasma according to the differential equation

$$\frac{dx}{dt} = k_r a - k_a x \tag{3}$$

* Where a_r is the amount of drug released from the tablet at time t, it can be shown[9] that $a_r = a_o f_i + a_o f_r(1 - e^{-k_r t})$ where f_i is the fraction of the total drug released immediately.

or, substituting for a from equation (2)

$$\frac{dx}{dt} = a_o f_r k_r e^{-k_r t} - k_a x \tag{4}$$

Integration of equation (4), solving for the integration constant at $t = 0$, $x = a_o f_i$, gives

$$x = \frac{a_o f_r k_r}{(k_a - k_r)} (e^{-k_r t} - e^{-k_a t}) + a_o f_i e^{-k_a t} \tag{5}$$

At zero time the amount of drug in compartment B is zero, but the amount increases by absorption from the gastrointestinal tract and is decreased by excretion and/or metabolism according to the expression

$$\frac{db}{dt} = k_a x - k_e b - k_m b \tag{6}$$

or, after substitution for x from equation (5) and collecting terms,

$$\frac{db}{dt} = \frac{a_o f_r k_a k_r}{(k_a - k_r)} (e^{-k_r t} - e^{-k_a t}) + a_o f_i k_a e^{-k_a t} - (k_e + k_m) b \tag{7}$$

After integration, equation (7) gives

$$b = \frac{a_o f_r k_a k_r}{(k_a - k_r)(k_e + k_m - k_r)} (e^{-k_r t} - e^{-(k_e + k_m) t}) + \frac{a_o f_i k_a - \frac{a_o f_r k_a k_r}{(k_a - k_r)}}{(k_e + k_m - k_a)} (e^{-k_a t} - e^{-(k_e + k_m) t}) \tag{8}$$

Equation (8) is the desired expression for the amount of drug in the plasma and tissues (exclusive of drug in the gastrointestinal tract and urine) after administration of a sustained release preparation. If only plasma drug levels are to be obtained, no measure of individual values of k_e and k_m will be obtained, and these rate constants accounting for disappearance of drug from plasma can be combined into one parameter, k_d. If a_o is defined as the dose in mg/kg, b is mg of drug per kilogram body weight. Dividing the right side of equation (8) by the specific apparent volume of distribution,* V'_d, gives plasma concentration, $c = b/V'_d$. Incorporating these changes equation (8) becomes

$$c = \frac{a_o f_r k_a k_r}{V'_d (k_a - k_r)(k_a - k_r)} (e^{-k_r t} - e^{-k_a t}) + \frac{a_o f_i k_a - \frac{a_o f_r k_a k_r}{(k_a - k_r)}}{V'_d (k_d - k_a)} (e^{-k_a t} - e^{-k_d t}) \tag{9}$$

* Apparent volume of distribution[8, 10] has the dimension liters when the total dose is used. For doses in mg/kg, the volume of distribution is most readily obtained on a per kilogram basis, l/kg, and it is proposed that this be termed the specific apparent volume of distribution, V'_d defined as milligrams drug per kilogram body weight divided by plasma concentration in milligrams per liter. The definition should not be construed to exclude use of serum or whole blood, or the uniform substitution of weights other than in milligrams—this does not change the dimensions of V'_d from l/kg. Although the term has little physiological meaning when the value is greater than the total body water content per kilogram (indicating concentration in the extravascular spaces), values of V'_d in the range 0·1 to 0·7 indicate the available space in which the drug is distributed.

If an oral solution of drug, or a tablet or capsule designed to release its drug content essentially immediately, is administered, the plasma drug levels can be obtained from equation (9) by noting that under these conditions $f_r = 0$ and $f_i = 1$. Thus equation (9) reduces to

$$c = \frac{a_o k_a}{V'_d(k_a - k_a)} (e^{-k_a t} - e^{-k_a t}) \tag{10}$$

which is the same form derived previously for this case.[1, 2, 4, 6]

The fraction of a_o in the urine as a function of time will be given by $du/dt = k_e b$. Substitution from equation (8), integration and rearranging gives

$$u = a_o(f_i + f_r) \frac{k_e}{(k_e + k_m)} - \frac{a_o f_r k_a k_e}{(k_a - k_r)(k_e + k_m - k_r)} (e^{-k_r t} - \frac{k_r}{(k_e + k_m)} e^{-(k_e + k_m)t}) - \frac{a_o f_i k_e - \frac{a_o f_r k_e k_r}{(k_a - k_r)}}{(k_e + k_m - k_a)} (e^{-k_a t} - \frac{k_a}{(k_e + k_m)} e^{-(k_e + k_m)t}) \tag{11}$$

For oral solution of drug ($f_i = 1$, $f_r = 0$) this reduces to

$$u = a_o \frac{k_e}{(k_e + k_m)} - \frac{a_o k_e}{(k_e + k_m - k_a)} (e^{-k_a t} - \frac{k_a}{(k_e + k_m)} e^{-(k_e + k_m)t}) \tag{12}$$

If $f_i + f_r = 1$ equations (11) and (12) both reduce at t equal to infinity to $u = a_o k_e/(k_e + k_m)$, indicating that the fraction of the drug excreted is determined by the relative rates of excretion and metabolism.

EXPERIMENTAL AND RESULTS

HT1479 (1-(*o*-methoxyphenyl)-4-(γ-methoxypropyl)-piperazine phosphate)* was orally administered to mongrel dogs as an aqueous solution and in the form of a plastic-matrix type sustained release preparation in tablet form (Gradumet†). Food but not water was withheld on the day of the experiment. The same six dogs were used with both dosage forms, at least a week elapsing between experiments using the same animal. HT1479 sustained release tablets, 75 mg, were administered on the basis of one per kilogram or fraction of a kilogram, the average dose actually received being 79·0 mg/kg. The oral solution of HT1479 was then calculated to be one-half the sustained release dose, or 39·5 mg/kg, administered by stomach tube as a solution containing 39·5 mg/ml, followed by 10 ml of water. Blood samples of 10 ml were drawn just prior to dosing and ½, 1, 1½, 2, 3, 4 and 5 hr after dosing. Plasma samples of 4 ml were analyzed for HT1479 by the methyl orange procedure of Brodie and Udenfriend.[11] The plasma levels of HT1479 and the standard deviations are given in Table 1.

The *in vitro* release of HT1479 from the sustained release tablet (lot no. 709-8933) was determined by placing six HT1479 sustained release tablets and 300 ml distilled

* Covered in U.S. pat. 2,891,063, assigned to Abbott Laboratories.
† Gradumet is the registered trademark of Abbott Laboratories.

TABLE 1. HT1479 FREE BASE PLASMA CONCENTRATIONS (UG/ML) IN DOGS

	Time hr	668*	1059	711	816	1067	1069	Average ± S.D.
Solution, 39·5 mgPO_4 salt/kg, orally	0·5	10·12	1·10	5·03	3·50	3·50	5·80	4·84 ± 3·05
	1·0	7·60	3·23	7·00	6·76	6·26	4·53	5·90 ± 1·67
	1·5	7·00	3·93	6·77	6·60	5·67	3·90	5·64 ± 1·41
	2·0	6·95	3·87	7·43	5·50	5·33	2·53	5·27 ± 1·84
	3·0	5·05	3·37	5·23	3·60	3·56	1·10	3·65 ± 1·49
	4·0	4·42	3·30	4·13	4·26	3·16	0·73	3·33 ± 1·38
	5·0	3·98	2·37	3·63	2·50	2·23	0·10	2·47 ± 1·36
Sustained release tablets, 79·0 mg/PO_4 salt/kg, orally	0·5	0·35	1·25	1·65	0·70	3·05	2·42	1·57 ± 1·02
	1·0	2·18	3·75	3·42	3·15	3·05	4·28	3·30 ± 0·71
	1·5	4·20	4·70	6·55	4·50	4·00	3·75	4·62 ± 1·01
	2·0	4·55	4·20	7·08	4·95	4·13	3·84	4·79 ± 1·18
	3·0	5·98	5·68	7·08	5·20	7·25	4·88	6·01 ± 0·97
	4·0	6·25	4·95	6·88	6·10	6·53	4·50	5·87 ± 0·94
	5·0	5·45	4·25	5·78	5·03	6·36	4·12	5·16 ± 0·88

* Dog numbers.

water in a 600-ml wide-mouth bottle, rolling at 100 rpm at room temperature and taking, at various intervals, 10-ml aliquots for assay. The amount of drug released was calculated by correcting for the volume of solution present when the aliquot was removed and for the amount of HT1479 removed in previous aliquots. The per cent of drug released from the sustained release tablet was 20·4, 32·4, 68·0 and 88·0 at $\frac{1}{2}$, 1, 4 and 8 hr. Data are plotted semi-logarithmically in Fig. 1 with the least squares line calculated from the data.

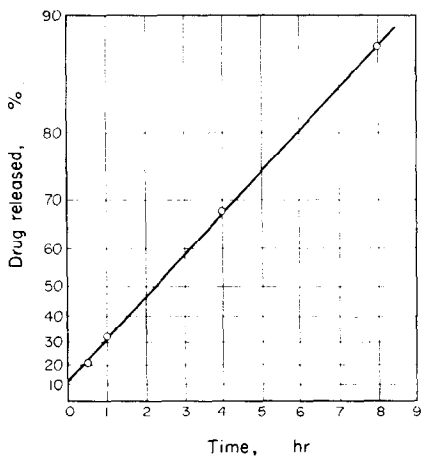


FIG. 1. *In vitro* release curve for 75 mg HT1479 sustained release tablets, with the least squares line from which the values $k_r = 0{\cdot}25\ hr^{-1}$, $f_i = 0{\cdot}12$ and $f_r = 0{\cdot}88$ are calculated.

DISCUSSION

The interpretation of plasma drug levels, following oral administration of a drug solution, in terms of two simultaneous apparent first order processes, has several advantages. One is that a smooth theoretical curve can be drawn through the experimental points, partly eliminating the subjective factor in fitting a curve to data. Extrapolation of plasma levels to times later than that for which experimental values

are available is also facilitated, and allows this to be done based on the data in the earlier time period. In addition to these graphic advantages, measures of the rates of absorption of the drug from the gastrointestinal tract and disappearance of the drug from plasma are obtained, and the order of the kinetics which describes the system is verified.

The apparent first order absorption and disappearance rates are calculated on the assumption that these processes are occurring in an apparent first order manner. Although for some drugs this has been demonstrated,[3, 5, 7, 8] the decision for a given drug in a given species must be based on whether or not the curve adequately fits the data. Fig. 2 shows that plasma levels of HT1479 following oral administration of

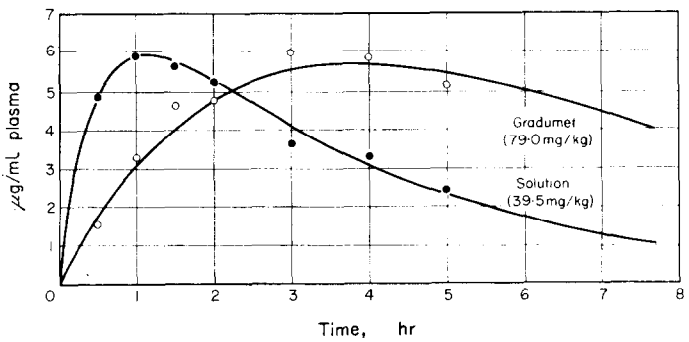


FIG. 2. Average plasma HT1479 free base concentrations from six dogs after administration of 39·5 mg PO_4 salt/kg as solution (●) and 79·0 mg PO_4 salt/kg as sustained release tablets (○). The curves are calculated according to equation (10) for solution with $a_o = 28{\cdot}8$ mg/kg and equation (9) for sustained release tablets with $a_o = 57{\cdot}6$ mg/kg, $k_r = 0{\cdot}25$, $f_i = 0{\cdot}12$, $f_r = 0{\cdot}88$, and the values in both equations of $k_a = 2{\cdot}0\ hr^{-1}$, $k_d = 0{\cdot}28\ hr^{-1}$ and $V'_d = 3{\cdot}52$ l/kg.

the solution to dogs are adequately described by a curve calculated from equation (10), and thus absorption and disappearance of HT1479 follow apparent first order kinetics. The apparent first order absorption constant, k_a, is 2·0 hr^{-1}, and the apparent first order constant which describes disappearance of drug from the plasma, k_d, is 0·28 hr^{-1}.

Disappearance of drug from the plasma is a complex phenomenon involving metabolism, excretion, and equilibration with tissues. Assigning a first order constant to the overall process assumes that metabolism and excretion are both first order processes or that one, if it is sufficiently greater in magnitude such that the other is negligible, is first order. On the basis of these assumptions no data are obtained to allow a measure of individual rates of metabolism or excretion. The steady state process of equilibration of drug between plasma and tissue is assumed to be rapid and therefore would not appreciably affect the values of k_a and k_d obtained. If equilibration were not sufficiently rapid to be neglected, it would influence the more rapid process more. This would be absorption in most cases, as it is for HT1479. The contribution from this source to the absorption constant is not readily determined, and this effect is usually neglected.

Calculation from equation (10) of the curve for plasma levels of HT1479 from solution, as shown in Fig. 2, was first done substituting the dose, 28·8 mg free base/kg, for a_o. By successive approximation the values of k_a, k_d and V'_d with time in hours

were determined to give the best fit to the data. Although the values of k_a, k_d and V_d' are mutually dependent to some degree, k_a primarily determines the slope of the ascending portion of the curve, k_d the slope of the descending portion, and V_d' the height of the whole curve. If one or two experimental points do not fall as close to the calculated curve as the others, but the curve closely approximates the remaining points, the value of the volume of distribution per kilogram, V_d', determined may be different than that calculated from the average theoretical amounts of drug present divided by the experimental plasma levels. Because of the excellent agreement between the theoretical and experimental plasma levels obtained with HT1479 solution, the value of the specific volume of distribution (volume of distribution per kilogram) used to obtain the curve shown in Fig. 2, 3·52 l/kg, is close to the average of the calculated values, 3·53 l/kg (see Table 2).

TABLE 2. SPECIFIC VOLUME OF DISTRIBUTION OF HT1479

Time, (hr)	Spec. vol. Dist. (l/kg)*	
	Solution	Sustained release tablets
0·5	3·47	3·92
1·0	3·52	3·30
1·5	3·61	3·11
2·0	3·52	3·52
3·0	3·94	3·24
4·0	3·28	3·40
5·0	3·34	3·72
average ± S.D.	3·53 ± 0·21	3·46 ± 0·28

* Calculated as theoretical mg drug/kg (from $b = cV_d'$ and equations (9) and (10)) divided by average experimental plasma levels (mg/l).

Absorption of drug and disappearance of drug from the plasma should be governed by the same rate constants when HT1479 is administered in sustained release form, with the possible exception that the absorption rate constant may vary with the level of the gastrointestinal tract at which absorption takes place. Calculation of the theoretical plasma curve according to equation (9) for plasma levels following administration of the sustained release tablets was therefore based on the same values of k_a and k_d used to calculate the plasma curve for the solution experiment. Values of the apparent first order release constant (k_r) and f_i and f_r were the same as calculated from the least squares line fit to the *in vitro* release curve of the sustained release tablet[9] (see Fig. 1). The volume of distribution per kilogram used in the calculation was the same as was used in the calculation for the plasma curve following administration of HT1479 solution (3·52 l k/g). The dose, a_o, was 57·6 mg of the free base per kilogram (equivalent to 79·0 mg of the phosphate salt per kilogram). The curve obtained is given in Fig. 2 with the average experimental points.

The values for the specific volume of distribution calculated from theoretical body drug content and experimental plasma concentrations following administration of sustained release tablets are given in Table 2. The average value, 3·46 l /kg, is not

significantly different from the value used in calculation of the curve (3·52 1/kg). The height of the calculated curve is close to the experimental plasma levels, as shown by the average volume of distribution, indicating that the drug is available from the sustained release tablet and is absorbed from the gastrointestinal tract at the levels where it is released.

The calculated curve fits the experimental points with adequate precision to suggest that the assumptions on which equation (9) is based are operative. The release characteristics of the sustained release tablet *in vivo* are therefore essentially the same as determined *in vitro* in aqueous solution. Changing the value of k_r to 0·28 hr^{-1} in equation (9) gives a curve* which fits the data as well as $k_r = 0{\cdot}25$ hr^{-1}, but values outside the range 0·25–0·28 hr^{-1} lead to progressively larger values of the sum of the squares of the deviations.

Excretion studies should provide estimates of absorption and disappearance of drug from the plasma using equation (11) or (12). In addition, an estimate of the excretion rate and metabolism rate may be obtained from the asymtotic value of the cumulative excretion curve. The accuracy of the values of the absorption rate, and also of release characteristics of sustained release preparations, will decrease, however, because the system used to measure these values is one compartment further away from these phenomena than when using plasma levels.

* When the rate constants k_r and k_d are equal equation (9) reduces[4] to

$$c = \frac{a_o f_r k_a k t}{V_d' (k_a - k)} e^{-kt} + \frac{a_o f_i k_a - \frac{a_o f_r k_a k}{(k_a - k)}}{V_d' (k_a - k)} (e^{-kt} - e^{-k_a t}), \text{ where } k_r = k_d = k.$$

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