Pharmacokinetics of Accumulation

By J. M. VAN ROSSUM

The rate and degree of drug accumulation following multiple fixed interval dosage schedules is calculated from the average plasma water concentration of drug per dosage interval. The degree of accumulation is determined by the dose, the distribution volume, the biological half-life, and the dosage interval. The rate of accumulation is mainly determined by the biological half-life. Accumulation to 90 percent of the plateau is reached after a time interval of 3.3 times the biological half-life.

CHRONIC ADMINISTRATION of a drug to patients may lead to a gradual increase in blood levels until finally a steady-state condition is reached. Accumulation occurs if drug intake exceeds elimination which may be the case when a drug is repeatedly administered in fixed doses at fixed intervals (3, 9–11). Accumulation is most evident for drugs which are slowly eliminated such as bromides and digitoxin (1).

In case of multiple dosing of drugs it is of importance to know the rate with which drug accumulation occurs and the plasma level that is attained at the plateau. The average plasma concentration at the plateau may be calculated by an equation presented by Wagner (9). The rate of drug accumulation has not been calculated.

In this paper the kinetics of drug accumulation with respect to both the rate and the degree of accumulation is presented.

MATHEMATICS OF DRUG ACCUMULATION

Most drugs are administered by oral or rectal routes. Assuming the operation of first-order kinetics, the drug concentration in the plasma water after administration of a single dose of a drug (A) may be given in the following equation (3, 8):

$$C_A = C_{Am}\,(e^{-t/\tau_2} - e^{-t/\tau_1}) \qquad \text{(Eq. 1)}$$

Here C_A is the plasma water concentration at the time t after administration, τ_1 and τ_2 are time constants for absorption and elimination, while C_{Am} is a constant depending on the dose Q_A^0, the volume of distribution V_1, and the time constants [$C_{Am} = Q_A^0 \cdot \tau_2/(\tau_2 - \tau_1)V_1$].

The biological half-life is directly related to the time constant for elimination ($t_{1/2} = 0.693 \cdot \tau_2$).

During administration of a drug on a multiple fixed dosage schedule such that a fixed dose Q_A^0 is given after a fixed time interval Δt, the plasma water concentration may be presented by the following equation (3):

$$C_{A(j)} = C_{Am}\left(\frac{1 - e^{-j\cdot\Delta t/\tau_2}}{1 - e^{-\Delta t/\tau_2}} \cdot e^{-t/\tau_2} - \frac{1 - e^{-j\cdot\Delta t/\tau_1}}{1 - e^{-\Delta t/\tau_1}} \cdot e^{-t/\tau_1}\right) \qquad \text{(Eq. 2)}$$

Here $C_{A(j)}$ is the plasma water concentration in the j'th interval at the time t after administration of the j'th dose ($j = 1$ for the first interval). Equation 2 has been called the accumulation equation (6).

The plasma water concentration of a theoretical drug A administered on a fixed multiple-dosage schedule as calculated with Eq. 2 is given in Fig. 1. It is obvious that for large values of j Eq. 2 acquires a limit which is the concentration for each interval at the steady-state situation:

$$C_{A(pl)} = C_{Am}[e^{-t/\tau_2}/(1 - e^{-j\cdot\Delta t/\tau_2}) - e^{-t/\tau_1}/(1 - e^{-j\cdot\Delta t/\tau_1})] \qquad \text{(Eq. 3)}$$

Here $C_{A(pl)}$ is the plateau plasma water concentration at the time t after administration of a dose. The plasma water concentration at the plateau therefore oscillates between a minimum value (when $t = 0$) and a maximum value (3, 6). (See also Fig. 1.)

The rate of accumulation could be calculated from Eqs. 2 and 3 by computing the time ($j.\Delta t$) at which the plateau is reached for 90 or 95%. The combination of Eqs. 2 and 3 leads however to complicated relations. A simple relation may be obtained from equations for the average plasma water concentration over each Δt interval.

The average plasma water concentration in the j'th interval may be obtained by integration of Eq. 2 for each Δt interval and division of the result by Δt, as shown by the following equation:

$$\bar{C}_{A(j)} = \frac{1}{\Delta t} \cdot \int_0^{\Delta t} C_{A(j)}\,dt = \frac{C_{Am}}{\Delta t}\,[\tau_2(1 - e^{-j\cdot\Delta t/\tau_2}) - \tau_1(1 - e^{-j\cdot\Delta t/\tau_1})] \qquad \text{(Eq. 4)}$$

Here $\bar{C}_{A(j)}$ is the average plasma water concentration in the j'th interval. The average plasma water concentration of two theoretical drugs administered on a fixed multiple-dosage schedule as calculated with Eq. 4 is given in Fig. 2. It may be seen that the plateau is reached earlier when the half-life is shorter.

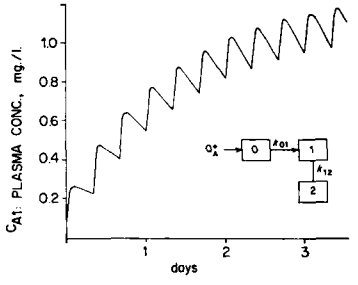

Fig. 1—An accumulation curve as calculated with Eq. 2 of the plasma water concentration following multiple dosing of a drug A ($\tau_1 = V_0/k_{01}$ *and* $\tau_2 = V_1/k_{12}$). *Dosage regimen, t.i.d.:* $\Delta t = 8$ *hr. Dose: 10 mg.;* $t_{1/2} = 24$ *hr.* $V_0 = 6$ *l.;* $V_1 = 36$ *l.;* $k_{01} = 12$ *l./hr.;* $k_{12} = 1.04$ *l./hr.;* $\tau_1 = 0.5$ *hr.;* $\tau_2 = 34.6$ *hr.*

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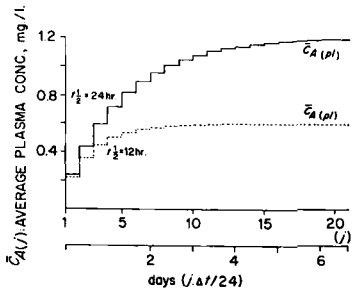

Fig. 2—Average plasma water concentration calculated with Eq. 4 following multiple dosing of two drugs with half-lives of 24 and 12 hr., respectively. The accumulation plateau is directly proportional to the biological half-life while the rate of accumulation is inversely proportional to $t_{1/2}$. *In this case* $\tau_1 = 0.2$ *hr. Dosage regimen, t.i.d.:* $\Delta t = 8$ *hr. Dose: 10 mg.*

Equation 4 reduces to the following equation for large j values, thus representing the average plasma water concentration at the plateau:

$$\bar{C}_{A(pl)} = \frac{C_{Am}}{\Delta t}(\tau_2 - \tau_1) = 1.44\,\frac{Q_A^0}{V_1}\cdot\frac{t_{1/2}}{\Delta t} \quad \text{(Eq. 5)}$$

This equation, which represents the degree of accumulation, is identical to that presented by Wagner *et al.* (9) and is discussed in detail by Krüger-Thiemer (6).

The rate of accumulation may be calculated from a combination of Eqs. 4 and 5:

$$\bar{C}_{A(j)} = \bar{C}_{A(pl)}\cdot\left(1 - \frac{\tau_2}{\tau_2 - \tau_1}\,e^{-j\,\cdot\,\Delta t/\tau_2} + \frac{\tau_1}{\tau_2 - \tau_1}\,e^{-j\,\cdot\,\Delta t/\tau_1}\right) \quad \text{(Eq. 6)}$$

The second exponential term of Eq. 6 is small with respect to the first one if $\tau_2 > \tau_1$. This implies that in such cases Eq. 6 reduces to the following equation:

$$\bar{C}_{A(j)} = \bar{C}_{A(pl)}\left(1 - \frac{\tau_2}{\tau_2 - \tau_1}\,e^{-j\,\cdot\,\Delta t/\tau_2}\right) \quad \text{(Eq. 7)}$$

It may be seen from this equation that the rate of accumulation largely is determined by the time constant for elimination and therefore by the biological half-life, and is dependent of the type of dosage regimen. See also Fig. 2.

It follows from Eq. 7 that the logarithm of the accumulation deficit, $\log\,[1 - \bar{C}_{A(j)}/\bar{C}_{A(pl)}]$, is linearly related to the time $(j\cdot\Delta t)$ after the start of the dosage schedule as may be seen from the following equation:

$$\log\,[1 - \bar{C}_{A(j)}/\bar{C}_{A(pl)}] = -0.301\,j\,\cdot\,\Delta t/t_{1/2} + \log\,[\tau_2/(\tau_2 - \tau_1)] \quad \text{(Eq. 8)}$$

The slope of the straight line representing the logarithm of the accumulation deficit as a function of time $(j\cdot\Delta t)$ is merely determined by the half-life. This relationship as calculated from Eq. 8 for two theoretical drugs is given in Fig. 3. It may be seen from this figure and Eq. 8 that the rate of accumulation does not depend on the dosage interval, but only depends on the $t_{1/2}$ value.

The rate of accumulation may be expressed in terms of a time constant for accumulation or as an accumulation half-life ($tc_{1/2}$). The latter may be obtained from Eq. 8 by computation of $j\cdot\Delta t$ for the case that $\bar{C}_{A(j)}/\bar{C}_{A(pl)}$ equals 0.5 (7):

$$tc_{1/2} = t_{1/2}[1 + 3.30\,\log\,\tau_2/(\tau_2 - \tau_1)] \quad \text{(Eq. 9)}$$

The accumulation half-life therefore is independent of the dosage interval and is directly proportional to $t_{1/2}$, it approaches to $t_{1/2}$ for $\tau_2 \gg \tau_1$ or $\tau_1 \to 0$. This is generally the case for drugs with long half-lives ($t_{1/2} > 12$ hr.) and always so in case of intravenous administration. This approximation does not hold for sustained-release preparations.

The plateau plasma concentration is practically reached after such a time interval $(j\cdot\Delta t)$ since $C_{A(j)}$ equals 0.9 or 0.95 of $C_{A(pl)}$. For clinical purposes it may be stated that the plateau is reached after a time equal to 3–4 times the biological half-life. The accumulation half-life, the number of doses, and the time for accumulation to 90% of the plateau as related to the biological half-life and the dosage interval are given in Table I.

RESULTS AND DISCUSSION

The gradual increase of the plasma concentration of desipramine following a fixed multiple-dosage schedule of 25 mg. t.i.d. in a single patient is given in Fig. 4 (4). In this patient the accumulation plateau is reached after 5 days. The logarithm of the accumulation deficit as a function of time results in a straight line from which the biological half-life may be calculated (see Fig. 5). The $t_{1/2}$ in this patient is 33 hr. From the data for different patients receiving the same drug (4) it follows that the accumulation plateau is reached sooner when the half-life is shorter. Variation in the biological half-life for humans and animals thus results in a variation of the plateau level as well as the rate of accumulation.

Since many drugs may cause an induction of drug metabolism (2) the half-life of a drug may decrease during the drug treatment. Consequently elimination may occur at a higher rate after cessation of chronic dosing.

For most drugs the biological half-life merely determines the accumulation rate. If excessive plasma protein binding occurs the apparent half-life is shorter when the plasma concentration is higher (5). This implies that deviation may occur from the equations derived above.

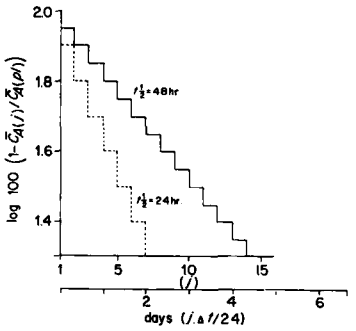

Fig. 3—Logarithm of the accumulation deficit as function of time for two drugs as calculated with Eq. 8. The slope of the straight line is inversely proportional to the biological half-life. Dosage regimen, t.i.d.: $\Delta t = 8$ *hr. Dose: 10 mg.*

TABLE I—THE RELATIONSHIP BETWEEN THE BIOLOGICAL HALF-LIFE, THE DOSAGE INTERVAL, THE RATE OF ACCUMULATION AND THE AVERAGE PLASMA CONCENTRATION AT EQUILIBRIUM FOLLOWING CHRONIC DRUG ADMINISTRATION[a]

Dosage Interval Δt, hr.	Biological Half-life $t_{1/2}$, hr.	Accumulation Half-time $t_{c1/2}$, hr.	Av. Plateau Concn. $\bar{C}_{Apl}$, mg./l.	Number of Doses for 90% of Plateau Value N	Time for Reaching a Plasma Concentration of 90% of the Plateau Value Days	hr.	min.
1	3	3.79	1.20	11		10	45
2	3	3.79	0.60	5		10	45
1	6	6.75	2.40	21		20	40
2	6	6.75	1.20	10		20	40
3	6	6.75	0.80	7		20	40
4	6	6.75	0.60	5		20	40
4	12	12.74	1.20	10	1	16	35
6	12	12.74	0.80	7	1	16	35
8	12	12.74	0.60	5	1	16	35
4	24	24.73	2.40	20	3	8	
6	24	24.73	1.60	13	3	8	
8	24	24.73	1.20	10	3	8	
12	24	24.73	0.80	7	3	8	
6	48 (2d)	48.72	3.21	27	6	16	
8	48 (2d)	48.72	2.40	20	6	16	
12	48 (2d)	48.72	1.60	13	6	16	
24	48 (2d)	48.72	0.80	7	6	16	
8	96 (4d)	96.72	4.81	40	13	7	
12	96 (4d)	96.72	3.21	27	13	7	
24	96 (4d)	96.72	1.60	13	13	7	
12	144 (6d)	144.72	4.81	40	19	23	
24	144 (6d)	144.72	2.40	20	19	23	
24	192 (8d)	192.72	3.21	27	26	14	
24	288 (12d)	288.71	4.81	40	39	22	

[a] The initial and maintenance dose has been fixed at 10 mg., the volume of distribution at 36 l., and the time constant for resorption $\tau_1 = 0.72$ hr.

The calculation of the average plateau plasma concentration by Eq. 5 is based on the assumption of irreversible first-order processes for absorption and elimination. This equation is not valid if absorption process is a reversible first-order process with clearance constants k_{01} and k_{10}. The time constants τ_1 and τ_2 then are no longer inversely proportional to k_{01} and k_{12} but also dependent on k_{10}. The constant C_{Am} in that case is also different $[C_{Am} = Q_A^0/(\tau_2 - \tau_1)k_{12}]$. The average plasma water concentration at the plateau is then given by the following equation:

$$\bar{C}_{A(pl)} = Q_A^0/k_{12} \cdot \Delta t \qquad \text{(Eq. 10)}$$

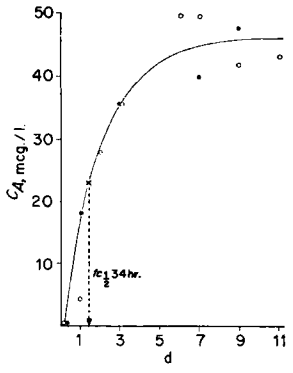

Fig. 4—Accumulation curve of desipramine following chronic administration of 25 mg. 3 times a day to a patient. Data after Hammer et al. *(4). The curve is the result of two experiments. The second experiment (●) is made 5 weeks after the first (○). Accumulation to 90% of the plateau is reached within 5 days. Desipramine, 25 mg. Dosage regimen, t.i.d.: Δt = 8 hr.*

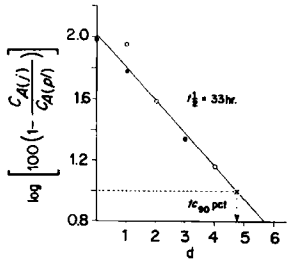

Fig. 5—Logarithm of the accumulation deficit of desipramine as a function of time. Data after Hammer et al. *(4). From the straight line the half-life of the accumulation is found to be 33 hr. for this patient.*

The clearance constant, k_{12}, may be obtained from plasma curves after intravenous administration of a drug. The equation for the accumulation rate remains valid, however in case of reversible absorption also.

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Keyphrases

Drug accumulation—pharmacokinetics
Pharmacokinetic equations—drug accumulation
Accumulation plateau—drug, multiple doses

Gas Chromatographic Determination of Hexachlorophene in Blood and Urine

By R. S. BROWNING, JR., JOHN GREGO, and H. P. WARRINGTON, JR.*

A rapid and convenient gas chromatographic technique has been developed for the determination of traces of hexachlorophene in human blood and urine. After a simple extraction, the hexachlorophene is acetylated. The acetyl derivative chromatographs well on conventional columns at a temperature within the operating range of a tritium foil electron capture detector.

ALTHOUGH HEXACHLOROPHENE (2,2′-methylene bis(3,4,6-trichlorophenol) is widely used in cosmetic preparations and pharmaceuticals, few methods are available for the determination of very low levels in blood or other tissue. Johnston and Porcaro (1) have described a method in which the hexachlorophene, after a relatively complex extraction procedure, is measured by colorimetry with 4-amino antipyrine as reagent. Using their method, as little as 20 mcg. of hexachlorophene can be measured in up to 100 g. of tissue. Wit and Van Genderen (2) used a similar technique in studying the recovery of hexachlorophene from the urine, feces, and milk of cattle dosed with the drug. Recovery data were reported for samples of various sizes, from a fraction of a gram for feces to 25 ml. for milk, containing 10–110 mcg. of drug. In another part of the same study, radiochemical assay methods were used to determine hexachlorophene in the excreta of rats and rabbits dosed with labeled drug.

Porcaro (3) has also described a gas chromatographic procedure for the determination of various bisphenols, including hexachlorophene. The minimum measurable quantity was claimed to be 5–10 mcg. He mentioned, but did not investigate, the potential increase in sensitivity which could result from the use of an electron capture detector. More recently, Wisniewski (4) has reported a gas chromatographic method for the determination of hexachlorophene in soap. In contrast to Porcaro's approach, in which the unmodified phenol was injected on a short, specialized column with a relatively high liquid loading, Wisniewski first prepared the trimethylsilyl derivative in order to reduce tailing and sample loss on the more conventional column he used. He, too, used a flame-ionization detector.

On columns available to the authors, using temperatures and liquid phases compatible with the use of a tritium foil electron capture detector, direct injection of hexachlorophene was unsatisfactory. Instrument response to samples in the subnanogram range was erratic. This variability was largely explained when it was definitely established that fractional amounts of hexachlorophene samples were held in the instrument. Derivatives which could eliminate this problem were therefore investigated. In this laboratory, silyl derivatives were not wholly satisfactory. Detector response at low levels continued to be somewhat erratic, and the retention times for the derivatives were undesirably long. Acetylation, however, proved to be rapid, simple, and reproducible, and the diacetyl derivative chromatographed reliably on several substrates, including a silicone gum (SE-30), a silicone oil (OV-17), and an organosilicone polymer (EGSP-Z).

On the basis of these results, a sensitive gas chromatographic method for the determination of hexachlorophene in extracts from whole blood and urine has now been developed. Using the procedure described here, it is easy to measure hexachlorophene at levels down to 0.05 mcg./ml.

EXPERIMENTAL

Reagents—USP grade hexachlorophene obtained from Winthrop Laboratories was used without further purification. All other materials were reagent grade, obtained from recognized suppliers.

Apparatus—All the glassware used was cleaned before use by soaking in a 1:1 mixture of 6 *N* HCl and methanol for about 0.5 hr., then rinsing with distilled water. Glassware was oven-dried. An F and M (Avondale, Pa.) model 400 gas chromatograph equipped with a tritium foil electron capture detector was used for the chromatography. The 121.9-cm. (4-ft.) long 0.635-cm. (0.25-in.) diameter column was packed with 1% EGSP-Z on 100/120 mesh Gas-Chrom Q (Applied Science Labs, Inc., State College, Pa.). The oven temperature was 205–210°,

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