Rate of accumulation and plateau plasma concentration of drugs after chronic medication

SIR,—The plasma concentration of a drug reaches a steady state level after long-term administration of a fixed dose at fixed time intervals (Boxer, Jelinek & others, 1948; Augsberger, 1954; Krüger-Thiemer, 1960; Krüger-Thiemer & Bunger, 1961).

Assuming the operation of first order kinetics for such a dosage regimen (Teorell, 1939; Dost, 1953) the plasma concentration of a drug A during the intervals when it maintains a plateau blood level can be expressed by the following equation (Dost, 1953; Rossum & Tomey, 1968):

$$C_{A(pl)} = C_{Am}[e^{-t/\tau_2}/(1 - e^{-\Delta t/\tau_2}) - e^{-t/\tau_1}/(1 - e^{-\Delta t/\tau_1})] \quad .. \quad (1)$$

Here $C_{A(pl)}$ is the plasma concentration, τ_1 the time constant for absorption, τ_2 the time constant for elimination, Δt the fixed dosage interval, t the time from the commencement to the end of each interval (from time 0 to Δt) and C_{Am} a constant depending on the dose Q_A^0, the apparent volume of distribution V and the time constants [$C_{Am} = Q_A^0.\tau_2/(\tau_2 - \tau_1)V$].

The plateau concentration therefore oscillates between a minimum value (when $t = 0$) and a maximum value (Dost, 1953; Krüger-Thiemer & Bunger, 1961; Wiegand, Buddenhagen & Endicott, 1963).

The average plateau plasma concentration of the drug over a time interval Δt may be obtained by integration of $C_{A(pl)}$ over the interval Δt and subsequent division by Δt, as shown in the following equation:

$$\bar{C}_{A(pl)} = \frac{1}{\Delta t}\cdot\int_0^{\Delta t} C_{A(pl)}dt = \frac{C_{Am}}{\Delta t}(\tau_2 - \tau_1) = \frac{Q_A^0}{V}\cdot\frac{\tau_2}{\Delta t} \quad .. \quad (2)$$

This equation is identical to that of Wagner, Northam & others (1965) and discussed by Krüger-Thiemer (1966).

Since the biological half-life of the drug corresponds to τ_2 as $t_{\frac{1}{2}} = 0{\cdot}693\ \tau_2$, the average plateau plasma concentration may also be written as:

$$\bar{C}_{A(pl)} = 1{\cdot}44\,.\,\frac{Q_A^0}{V}\cdot\frac{t_{\frac{1}{2}}}{\Delta t} \quad .. \quad .. \quad .. \quad .. \quad (3)$$

The value Q_A^0/V may be calculated from a plasma concentration curve after administration of a single dose. In addition, such a curve also provides information about the degree of absorption (Krüger-Thiemer, 1960, 1966). The plateau concentration is directly proportional to the maintenance dose and half-time for elimination and is inversely proportional to the dosage interval and the volume of distribution.

The time, $tc_{\frac{1}{2}}$, which the average plasma concentration takes to reach half the average plateau concentration provides a measure of the rate of accumulation of the drug. A calculation of $tc_{\frac{1}{2}}$ is possible from an equation representing the average plasma concentration of each dosage interval; for example that for the j^{th} interval is given by the following equation (8):

$$\bar{C}_{A(j)} = \frac{C_{Am}}{\Delta t}[\tau_2(1 - e^{-j.\Delta t/\tau_2}) - \tau_1(1 - e^{-j.\Delta t/\tau_1})] \quad .. \quad (4)$$

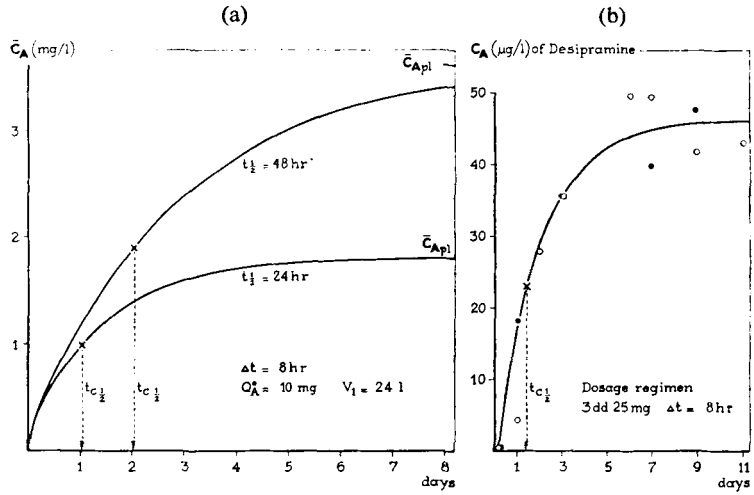

FIG. 1. Drug accumulation curves. (a) The average plasma concentration of two drugs with biological half-lives of 24 and 48 hr after a fixed multiple dosage regimen as calculated from equation (4). The plateau level is proportional to the biological half-life while also the rate of accumulation is practically proportional to $t_{\frac{1}{2}}$. (b) Plasma concentration of desipramine in a patient receiving a dose of 25 mg three times a day (Δt = 8 hr). The accumulation curve has been obtained by combining data of Hammer & others (1967) determined in two different accumulation experiments, made several weeks apart.

TABLE 1. THE PLATEAU LEVEL AND RATE OF DRUG ACCUMULATION. The average plateau plasma concentration obtained ($\bar{C}_{A(pl)}$), the half-time for accumulation ($tc_{\frac{1}{2}}$) and the time for accumulation of the drug to 90% of the plateau level ($tc_{90\%}$) have been calculated from equation (5). The calculations are based on the administration of a fixed dose of drugs (Q^0_A = 10 mg) in a multiple dosage regimen, a volume of distribution (V = 36 litres i.e. sum of extra- and intracellular fluid in a normal man), the time constant for absorption is kept constant for all drugs (τ_1 = 0·72 hr) while the biological half-life ($t_{\frac{1}{2}}$) and the dosage interval (Δt) is varied.

$t_{\frac{1}{2}}$ (hr)	Δt (hr)	$\bar{C}_{A(pl)}$ (mg/l)	$tc_{\frac{1}{2}}$ (hr)	$tc_{90\%}$ (hr)
3	1	1·20	3·79	10·8
6	2	1·20	6·76	20·7
6	4	0·60	6·76	20·7
12	4	1·20	12·74	40·6
12	8	0·60	12·74	40·6
24	4	2·41	24·73	80·5
24	8	1·20	24·73	80·5
24	12	0·80	24·73	80·5
48	8	2·41	48·73	160·2
48	12	1·60	48·73	160·2
96	12	3·21	96·74	319·7
96	24	1·60	96·74	319·7

The average plasma concentrations of two drugs with $t_{\frac{1}{2}} = 24$ and 48 hr calculated from this equation are shown in Fig. 1a. An experimental accumulation curve of desipramine administered to a patient 3 times per day ($\Delta t = 8$hr) for 11 days, and based on the data of Hammer, Ideström & Sjöqvist (1967), is presented in Fig. 1b. The $tc_{\frac{1}{2}}$ calculated from this experiment in this patient is 33 hr.

Since $tc_{\frac{1}{2}} = j.\Delta t$ when $\bar{C}_{A(j)} = 0{\cdot}5\ \bar{C}_{A(pl)}$ the accumulation half-time of a drug may be calculated by combining equations (2) and (4). The following equation is obtained if in addition $j\,.\,\Delta t \gg \tau_1$:

$$tc_{\frac{1}{2}} = t_{\frac{1}{2}}\,[1 + 3{\cdot}30 \log \tau_2/(\tau_2 - \tau_1)] \quad .. \quad .. \quad (5)$$

For most drugs especially those with a biological half-life of more than 12 hr $\tau_2 \gg \tau_1$, this equation can generally be reduced to $tc_{\frac{1}{2}} = t_{\frac{1}{2}}$. This implies that the half-time for accumulation of a drug is approximately equal to its half-time for elimination and is independent of the dosage interval. The drug accumulation is anticipated to have reached its plateau after a time-interval equal to $3\frac{1}{2}$ times the biological half-life (see Table 1). So far a drug with an elimination half-time of 2 days given by a multiple fixed dosage regimen, accumulation occurs at such a rate that the plateau plasma concentration is reached after one week.

The computed plateau plasma concentration half-times for accumulation, and the times at which the plateaux are practically reached are presented for a number of drugs in Table 1.

It may be concluded that the biological half life provides a good approximation of the degree of accumulation. This conclusion has special importance for patients receiving long term medication.

A full discussion of consequences and a detailed mathematical analysis of the equations are in the press (Rossum & Tomey, 1968).

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