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STEADY-STATE CONCENTRATIONS OF DRUGS WITH SHORT HALF-LIVES WHEN ADMINISTERED IN ORAL SUSTAINED RELEASE FORMULATIONS

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SUMMARY

Recognizing that the time available for drug absorption after oral administration is limited, and assuming an effective absorption time of 9–12 h, we have calculated the ratio of maximum to minimum drug concentrations in plasma at steady-state for drugs with different elimination half-lives given in sustained release products that release the drug in a first-order manner with a half-life of 3 or 4 h. The results suggest that drugs with relatively short elimination half-lives ($\leqslant$ 6 h) and low therapeutic indices ($\leqslant$3) must be given no less frequently than every 12 h. Drugs with pronounced multicompartment characteristics after oral dosing may need to be given at dosing intervals considerably shorter than their biologic half-lives unless they are administered in a sustained release formulation.

INTRODUCTION

The therapeutic index (TI) of a drug has classically been defined as the ratio of the median toxic or lethal dose to the median effective dose (Goldstein et al., 1974). For clinical purposes, a better definition is the ratio of the maximum drug concentration in plasma at which the patient is relatively free of adverse effects of the drug to the minimum drug concentration in plasma required to elicit a minimally adequate therapeutic response. In principle, a drug should be given with sufficient frequency so that the ratio of maximum to minimum drug concentrations in plasma at steady-state is less than the therapeutic index and at a high enough dose to produce effective concentrations. For a linear, one-compartment system with repetitive i.v. dosing (constant dose, constant dosing interval, τ) the ratio of maximum to minimum drug concentrations in plasma at steady-state is given by

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$$\frac{C_{max}^{ss}}{C_{min}^{ss}} = e^{K\tau} \quad (1)$$

where K is the first-order elimination rate constant. It follows that

$$e^{K\tau} \leqslant TI \quad (2)$$

and

$$\tau \leqslant t_{1/2} \frac{\ln TI}{\ln 2} \quad (3)$$

where TI is the therapeutic index (Theeuwes and Bayne, 1977). When the therapeutic index of a drug is 2, the dosing interval should be equal to no more than one biologic half-life of the drug. For drugs with short elimination half-lives ($t_{1/2} \leqslant 6$ h) and low therapeutic indices ($TI \leqslant 3$), the proper dosing schedule may require the drug to be given unreasonably frequently. This situation prevails with theophylline in certain patients (Ginchansky and Weinberger, 1977) and with procainamide (Koch-Weser, 1977), among other drugs. Sustained release dosage forms may alleviate this problem since the slower the absorption of a drug the smaller the ratio of C_{max} to C_{min} over a dosing interval at steady-state. In theory a drug that must be given every 3 h at a dose (D) of 100 mg, can be given every 6 h (D = 200 mg), every 12 h (D = 400 mg) or every 24 h (D = 800 mg) simply by reducing the absorption rate constant of the drug to maintain the C_{max} to C_{min} ratio. This may be accomplished by modifying the formulation to reduce the release rate of drug compared to that of a conventional formulation. In fact, most commercially available sustained release products release drug in an apparent first-order fashion but at a considerably lower rate than oberved after conventional tablets or capsules.

A stringent limit on the dosing interval of oral formulations is imposed by the finite time over which a drug may be absorbed in the gastrointestinal tract. The literature on drug absorption, gastric emptying and intestinal motility suggests that within 9–12 h after administration, most drugs may be at a site in the intestine from which absorption is poor and ineffective (see, for example, Eve, 1966). With this effective absorption time range in mind, it follows that the maximum absorption half-life should be 3–4 h. Formulations which release drug more slowly are likely to result in unacceptably low bioavailability in a significant number of patients. In principle, a formulation that releases a well-absorbed drug in a first-order fashion with a half-life of 4 h will result in bioavailability ranging from 79 to 88% of the dose if absorption time is limited to 9–12 h. A formulation with a 3-h half-life for drug release yields availabilities of 88–94% of the dose over these absorption times. Shorter effective absorption times require still more conservative estimates of maximum absorption half-lives.

With these precepts in mind we have developed some general principles for frequency of dosing of drugs with relatively short elimination half-lives and low therapeutic indices administered in sustained release formulations, using the methods outlined below. We propose that adherence to these guidelines will generally allow one to maintain drug concentrations in plasma at steady-state within the therapeutic range without introducing serious bioavailability problems.

PHARMACOKINETIC CALCULATIONS

Assuming maximum absorption half-lives of 3 or 4 h, to ensure adequate availability, we have calculated C_{max} to C_{min} ratios at steady-state for drugs with elimination half-lives ranging from 1 to 6 h given at a dosing rate of 50 mg/h at intervals of 8, 12 or 24 h. The maximum concentration in plasma at steady-state was determined from

$$C^{ss}_{max} = \frac{D}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-Kt^{ss}_{max}} \tag{4}$$

assuming complete absorption, where

$$t^{ss}_{max} = \frac{2.3 \log[k_a(1 - e^{-K\tau})/K(1 - e^{-k_a\tau})]}{k_a - K} \tag{5}$$

and the minimum concentrations in plasma at steady-state from

$$C^{ss}_{min} = \frac{k_a D}{V(k_a - K)}\left[\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} - \left(\frac{1}{1 - e^{-k_a\tau}}\right) e^{-k_a\tau}\right] \tag{6}$$

D is the dose, V is the apparent volume of distribution (set at 10 liters), K is the first-order elimination rate constant, τ is the dosing interval, t^{ss}_{max} is the time at which drug concentration in plasma during a dosing interval at steady-state is at a maximum and k_a is the first-order absorption rate constant.

RESULTS AND DISCUSSION

The results are summarized in Tables 1 and 2. It is evident, in general, that drugs with short elimination half-lives and low therapeutic indices must be given no less frequently than every 12 h. In all cases, once-a-day dosing resulted in C^{ss}_{max} to C^{ss}_{min} ratios greater than 3. A sustained release formulation of procainamide, a drug with an average half-life of about 3 h and a therapeutic index of 2 in many patients, should probably be designed to be given no less frequently than every 8 h. Once-a-day dosing with sustained release dosage forms is appropriate for drugs with relatively high therapeutic indices or with relatively long elimination half-lives. However, the need for sustained release formulations of such drugs is not as great since adequate therapy can be achieved at reasonable dosing intervals.

The foregoing applies to drugs that display one-compartment model characteristics and where absorption is apparent first-order. Drugs with pronounced multicompartment characteristics after oral administration may show much larger C^{ss}_{max} to C^{ss}_{min} ratios than predicted by Eqn. 1. To illustrate this point we have calculated the C^{ss}_{max} to C^{ss}_{min} ratio for diazepam based on the pharmacokinetic parameters in one subject (subject 4) who received a 10 mg i.v. dose (Kaplan et al., 1973), using an equation appropriate for a three-compartment model (see Appendix), and assuming an absorption half-life of about 21 min (see Table 3). The drug had an elimination half-life of 33 h in this subject.

TABLE 1

CALCULATED STEADY-STATE PLASMA CONCENTRATIONS OF DRUGS WITH DIFFERENT ELIMINATION HALF-LIVES GIVEN IN A SUSTAINED RELEASE FORMULATION THAT RELEASES DRUG IN A FIRST-ORDER FASHION WITH A HALF-LIFE OF 3 h

Abbreviations: τ = dosing interval, t^{ss}_{max} = time at which drug concentration in plasma is at a maximum, C^{ss}_{max} = maximum drug concentration in plasma, C^{ss}_{min} = minimum drug concentration.

Elimination half-life (h)	Dose	τ	t^{ss}_{max}	C^{ss}_{max}	C^{ss}_{min}	$C^{ss}_{max}/C^{ss}_{min}$
1.98	400	8	2.6	17.3	9.5	1.8
	600	12	3.1	20.7	6.0	3.4
	1200	24	3.5	35.6	0.9	41.0
3.15	400	8	2.9	25.8	17.5	1.5
	600	12	3.6	29.4	12.8	2.3
	1200	24	4.3	46.4	3.0	15.3
4.01	400	8	3.0	31.9	23.5	1.4
	600	12	3.8	35.6	18.4	1.9
	1200	24	4.8	53.2	5.8	9.2
4.95	400	8	3.0	38.7	30.2	1.3
	600	12	4.0	42.4	24.8	1.7
	1200	24	5.2	60.3	9.8	6.2
5.97	400	8	3.1	46.1	37.5	1.2
	600	12	4.1	49.8	31.9	1.6
	1200	24	5.5	67.1	15.0	4.5

TABLE 2

CALCULATED STEADY-STATE PLASMA CONCENTRATIONS OF DRUGS WITH DIFFERENT ELIMINATION HALF-LIVES GIVEN IN A SUSTAINED RELEASE FORMULATION THAT RELEASES DRUG IN A FIRST-ORDER FASHION WITH A HALF-LIFE OF 4 h

Abbreviations: τ = dosing interval, t^{ss}_{max} = time at which drug concentration in plasma is at a maximum, C^{ss}_{max} = maximum drug concentration in plasma, C^{ss}_{min} = minimum drug concentration.

Elimination half-life (h)	Dose	τ	t^{ss}_{max}	C^{ss}_{max}	C^{ss}_{min}	$C^{ss}_{max}/C^{ss}_{min}$
1.98	400	8	2.7	16.5	10.6	1.6
	600	12	3.3	19.1	7.6	2.5
	1200	24	3.9	30.4	1.9	15.8
3.15	400	8	3.0	25.0	18.7	1.3
	600	12	3.8	27.7	14.8	1.9
	1200	24	4.9	40.4	4.9	8.2
4.01	400	8	3.1	31.2	24.8	1.3
	600	12	4.1	33.9	20.6	1.6
	1200	24	5.4	47.6	8.2	5.8
4.95	400	8	3.2	38.9	31.5	1.2
	600	12	4.2	40.7	27.1	1.5
	1200	24	5.9	54.7	12.8	4.3
5.97	400	8	3.2	45.4	38.9	1.2
	600	12	4.4	48.1	34.2	1.4
	1200	24	6.2	62.2	18.4	3.4

TABLE 3

CALCULATED MAXIMUM TO MINIMUM DIAZEPAM CONCENTRATION RATIOS IN PLASMA AT STEADY-STATE IN A SUBJECT WITH A 33-h ELIMINATION HALF-LIFE DURING DIFFERENT DOSING REGIMENS

Absorption half-life	Dose (mg)	Dosing interval (h)	$C^{ss}_{max}/C^{ss}_{min}$
21 min	30	24	3.1
21 min	10	8	1.5
2 h	30	24	2.1

According to Eqn. 1, once-a-day dosing should yield a C^{ss}_{max} to C^{ss}_{min} ratio of 1.66 if the drug were to have one-compartment characteristics. In fact, the ratio calculated for a dosing schedule of 30 mg once-a-day is about 3 (Table 3). Some drugs with these characteristics must be dosed at intervals considerably shorter than the biologic half-life to avoid adverse effects that are associated with high drug concentrations in the plasma (central compartment). In the case of diazepam, administration of 10 mg every 8 h may be expected to produce a C^{ss}_{max} to C^{ss}_{min} ratio, as shown in Table 3, that is close to that predicted by Eqn. 1 based on a 33-h elimination half-life, a one-compartment model and a dosing interval of 24 h. A reduction in the absorption rate constant of such drugs by appropriate formulation may substantially reduce the ratio of maximum to minimum drug concentrations in plasma at steady-state (see Table 3) and may permit considerably less frequent administration of the drug. In essence, the reduced absorption rate may eliminate the 'spike' of drug concentration in plasma associated with rapid absorption and slow distribution. The principal advantage of less frequent drug administration is the potential improvement in patient compliance with the prescribed regimen.

Pharmacokinetic theory suggests that the ultimate method for reducing the C_{max} to C_{min} ratio is to have zero-order absorption. Once steady-state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists. Several investigators have discussed the application of pharmacokinetic principles to the design of sustained release formulations that release drug in a zero-order fashion (Nelson, 1957; Rowland and Beckett, 1964; Robinson and Eriksen, 1966). An example of such a system is the elementary osmotic pump (Theeuwes, 1975). Such dosage forms, however, are still limited by considerations of effective residence time of drug at absorption sites in the gastrointestinal tract. Therefore, it is unlikely that a zero-order release formulation can be designed to release drug in the gut for more than 9–12 h without introducing bioavailability problems. Accordingly, the drug must be given no less frequently than two or three times a day if constant drug concentrations in plasma are to be maintained.

APPENDIX

The following equation was used to calculate values of drug concentrations in plasma (C) as a function of time (t) during a dosing interval at steady-state for a three-compartment open model with first-order absorption into the central compartment and first-

order elimination from the central compartment:

$$C = \frac{k_a FD(k_{21} - k_a)(k_{31} - k_a)}{V_c(\pi - k_a)(\alpha - k_a)(\beta - k_a)} \left[\frac{1}{1 - e^{-k_a\tau}}\right] e^{-k_a t}$$

$$+ \frac{k_a FD(k_{21} - \pi)(k_{31} - \pi)}{V_c(k_a - \pi)(\alpha - \pi)(\beta - \pi)} \left[\frac{1}{1 - e^{-\pi\tau}}\right] e^{-\pi t}$$

$$+ \frac{k_a FD(k_{21} - \alpha)(k_{31} - \alpha)}{V_c(k_a - \alpha)(\pi - \alpha)(\beta - \alpha)} \left[\frac{1}{1 - e^{-\alpha\tau}}\right] e^{-\alpha t}$$

$$+ \frac{k_a FD(k_{21} - \beta)(k_{31} - \beta)}{V_c(k_a - \beta)(\pi - \beta)(\alpha - \beta)} \left[\frac{1}{1 - e^{-\beta\tau}}\right] e^{-\beta t} \qquad \text{(A1)}$$

where k_a is the first-order absorption rate constant; k_{21} and k_{31} are first-order intercompartmental transfer rate constants; α, β and π are hybrid disposition constants such that $\pi > \alpha > \beta$; V_c is the volume of the central compartment, and F is the fraction of the administered dose (D) that reaches the central compartment.

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