ACCEPTABLE SAMPLING TIMES AT PLATEAU FOR DRUG ANALYSIS

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- 1 Two methods of estimating the average plasma drug concentration at plateau C_{av} are considered.
- 2 Given an acceptable error in the estimate of C_{av} , a range of sampling times, rather than a single time, during the dosing interval, can be calculated. This range depends on the variability of the half-life within the patient population, the dosing interval, the error in assay measurement and the therapeutic index of the drug.
- 3 When the minimum plasma drug concentration is monitored, an estimate of the individual's half-life is needed, unless the dosing interval is short. Then the population half-life may be used to obtain a reasonable estimate of C_{av} .

Introduction

When used as a guide to dosage adjustment during maintenance therapy, the target plasma drug concentration is often the time-averaged value at steady-state or plateau. This value is neither the maximum nor minimum but rather is given by the area under the plasma drug concentration-time curve, during a dosing interval at plateau, divided by the dosing interval (Wagner *et al.*, 1965).

Ethical and economic factors, amongst others, however, dictate against the frequent sampling of blood that is needed to accurately determine the average value. The most common approach, therefore, is to try to estimate this average value from the minimum of information, namely from a single plasma concentration value. Usually, the blood sample is taken just before the next dose is given, yielding the minimum or trough value. But as pointed out by Nicholson, Dobbs & Rodgers (1980) this may not be the ideal choice of sampling time. These workers show that, in the case of digoxin, the ideal sampling is 11 h after a daily dose. Similar calculations for other drugs, however, may lead to an inconvenient 'ideal' sampling time.

We consider, generally, the concept of an acceptable range of sampling times, rather than a single time, as well as the usefulness and limitations of the trough value.

Methods and results

Acceptable sampling times

Consider the case of a drug that exhibits linear one-compartment characteristics. If drug is administered extravascularly e.g. orally, it is assumed that absorption is rapid relative to elimination.

On a fixed dose and constant interval regimen the average drug concentration in plasma at plateau, C_{av} , is given by

$$C_{av} = \frac{F \cdot D_m}{Cl \cdot \tau} \quad (1)$$

where F is the bioavailability of the maintenance dose, D_m , taken at a fixed interval, τ , and Cl is the clearance of the drug.

Within the dosing interval at plateau, the plasma drug concentration fluctuates around the average value, the value at any time t being given by

$$C = \frac{F \cdot D_m}{V} \left[\frac{e^{-kt}}{1 - e^{-k\tau}} \right] \quad (2)$$

where k is the elimination rate constant of the drug and V is its volume of distribution.

Recalling that $Cl = k \cdot V$, the ratio C/C_{av} is therefore given by

$$\frac{C}{C_{av}} = \frac{k\tau \cdot e^{-kt}}{1 - e^{-k\tau}} \quad (3)$$

Equation (3) can be made general as follows. Commonly, in practice, the dosing interval is fixed. Let this value be some fixed multiple, n , of the population half-life, $\mu_{T/2}$, that is

$$\tau = n \cdot \mu_{T/2} = n \cdot 1n2/\mu_k \quad (4)$$

where μ_k is the population elimination rate constant. Similarly, let $t = n(t) \cdot \mu_{T/2}$. Further, recognising that an individual's elimination rate constant, k_i , will vary by some ratio, r , from the population value μ_k , it follows by appropriate substitution into equation (3), that

$$\frac{C}{C_{av}} = \frac{x \cdot e^{-n(t) \cdot \ln 2 \cdot r}}{1 - e^{-x}} \quad (5)$$

where $x = \ln 2 \cdot n \cdot r$.

Figure 1, which is a plot of the ratio C/C_{av} , when the dosing interval is one population half-life, for individuals with different elimination half-lives (between $0.33-3\mu T_{1/2}$) illustrates the general situation. Although the exact time when the concentration equals the average value varies, depending on the half-life in the individual, there is a time, at approximately 0.4 of the dosing interval, when all the concentrations are close to the average value. This then, would appear to be the ideal choice of sampling time. However, if one was to accept some error in the predicted value of C_{av} , say $\pm 20\%$, it is also clear that for the individual with a long half-life ($3\mu T_{1/2}$), any sampling time within the dosing interval would be acceptable. The range of acceptable times would obviously be much narrower for the individual who eliminates the drug more rapidly ($T_{1/2} = 0.33\mu T_{1/2}$). Since, for many drugs, there is no *a priori* reason to know the elimination half-life value in an individual before sampling, it follows that the selection of any acceptable range of sampling times must be based on the more rapid eliminators of the drug.

Estimates of the range of times within a dosing interval, $n(t)/n$, in which the plasma concentration lies within some acceptable range of C_{av} , for different values of the dosing interval, n , and the elimination rate constant, r , can be made upon rearrangement of equation (5). That is

Figure 1 Changes in the plasma drug concentration within a dosing interval at plateau, for subjects with different elimination half-lives (expressed as a multiple of the population value). In this example the dosing interval is one population half-life.

Figure 2 The range of sampling times, within a dosing interval at plateau, which gives a plasma drug concentration within a defined limit of the average value, as a function of the dosing interval. The heavy outer lines are the range of times when the acceptable limit is $\pm 20\%$ of the average value. The range narrows (inner faint lines) when measurement error ($\pm 10\%$) is also considered.

$$\frac{n(t)}{n} = \frac{1}{x} \ln \left[\frac{x}{(C/C_{av})(1 - e^{-x})} \right] \quad (6)$$

The bold outer lines in Figure 2 show this range when the acceptable error in estimating C_{av} is 20%. ($C = 0.8-1.2 C_{av}$), for the situation where the elimination half-life is three times shorter than the population value ($r = 3$). Even in this situation it can be seen that, if the drug is given frequently enough (n is small) virtually any time within the dosing interval is acceptable. Phenobarbitone is such an example, it is given once daily or three times a day and has a usual half-life of 5 days.

The acceptable range narrows as a drug is given less frequently. Analytical error in the measurement makes the practically acceptable range even narrower as shown by the faint continuous lines in Figure 2, constructed by assuming a measurement error of $\pm 10\%$. Also shown in Figure 2 (dotted line) is how the mid-point of the acceptable range varies. It is close to the mid-point of the dosing interval ($n \approx 0.5$), when drug is given frequently relative to its half-life (n is small), but gradually tends to the beginning of the dosing interval as the dosing interval is increased.

Sampling at the end of the dosing interval

It should be noted from Figure 2 that under practically no circumstance is the concentration at the end

Figure 3 Effect of dosing interval and half-life on the estimate of the average concentration calculated from the minimum concentration, assuming that the individual's half-life equals the population value.

of the dosing interval a good estimate of the average value. The exact relationship between this trough value, $C_{\min}$, and the average value is given by setting $t = \tau$ in equation (5),

$$C_{av} = \frac{C_{\min}}{\ln 2 \cdot n \cdot r} (e^{\ln 2 \cdot n \cdot r} - 1) \quad (7)$$

$$= \frac{1.44 C_{\min} (2^{nr} - 1)}{n \cdot r} \quad (8)$$

which indicates that C_{av} can only be calculated if the value of r (and hence the individual's half-life) is known. But $C_{\min}$ provides no estimate, per se, of the half-life. In the absence of such information it might be reasonable to assume that this is the population value, $\mu T_{1/2}$. Figure 3 shows the relationship between this estimated value of C_{av} , and the true C_{av} , as a

function of the dosing interval, for individuals whose elimination half-life varies from 0.33 to 3 times the population half-life value. It can be seen that, to produce an estimate of C_{av} within 20% of the true value, the dosing interval must be less than 30% of the population half-life for an individual with a half-life of 0.33 times the population value. While for a slow eliminator ($T_{1/2} = 3\mu T_{1/2}$) the dosing interval can be almost up to one population half-life before the error in estimating C_{av} becomes unacceptable.

Discussion

The preceding analysis indicates that trying to estimate the average plateau concentration from the minimum value is not as satisfactory as taking a blood sample sometime within the dosing interval. However, the difference between the two methods becomes small when the drug is given frequently (relative to its usual half-life). Then, the convenience of taking the sample just before the next dose may become the over-riding consideration. The acceptable range of sampling times depends on the range of half-lives within the patient population receiving the drug, the dosing interval and the acceptable error in the estimate of the average value. The range of half-lives of between 0.33–3 times the population value was chosen as it is likely to cover most situations. The acceptable error in estimating C_{av} depends mainly upon the therapeutic index of the drug, and consideration of the analytical error. For drugs with a narrow therapeutic index, the dosing interval is likely to be one population half-life or less, indicating that the ideal choice of a sampling time is around the mid-point of the dosing interval, with an acceptable range between 0.33–0.55 of that interval. Later times within this range are preferable because the likelihood of having achieved distribution equilibrium, when plasma concentration reflects that at the receptor site, is increased. Furthermore, if absorption is slow, either with conventional dosage forms or through design, such as with prolonged or controlled release products, then the acceptable range of sampling times will be even greater.

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