Pharmacokinetics made easy 11 Designing dose regimens

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D.J. Birkett, Professor of Clinical Pharmacology, Flinders University of South Australia, Adelaide
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Information from previous articles in this series can be used to design dose regimens.

1. Intravenous infusion and intermittent intravenous bolus dosing
Continuous intravenous infusions and intermittent intravenous boluses are common ways of administering drugs such as gentamicin, lignocaine and theophylline. Fig. 1 illustrates the plasma concentration time course of theophylline given intravenously. Given as a continuous infusion, the drug accumulates to a steady state concentration (C_{ss}) determined only by the dose rate and clearance (CL) (see Article 1 'Clearance' Aust Prescr 1988;11:12-3). The maintenance
dose rate to achieve a desired concentration can be calculated if the clearance is known.

equation 1

Desired concentration (C_{ss}) = maintenance dose rate / CL
The time to reach steady state is determined by the half-life (3-5 half-lives, see Article 3 'Half-life' Aust Prescr 1988; 11:57-9). If intermittent bolus doses are given every half-life (8 hours in this case for theophylline), half the first dose is eliminated over the first dosing interval. Therefore, after the second dose there are 1.5 doses in the body and half of this amount is eliminated before the third dose. The drug continues to accumulate with continued dosing until there is double the dose in the body, at which point the equivalent of one dose is eliminated each dosing interval (half-life). The plasma concentration is then at steady state (rate of administration equals rate of elimination where each is one dose per dosing interval). At steady state with a dosing interval equal to the half-life:

- the plasma concentration fluctuates two-fold over the dosing interval
- the amount of drug in the body shortly after each dose is equivalent to twice the maintenance dose
- the steady state plasma concentration averaged over the dosing interval is the same as the steady state plasma concentration for a continuous infusion at the same dose rate (see Fig. 1).

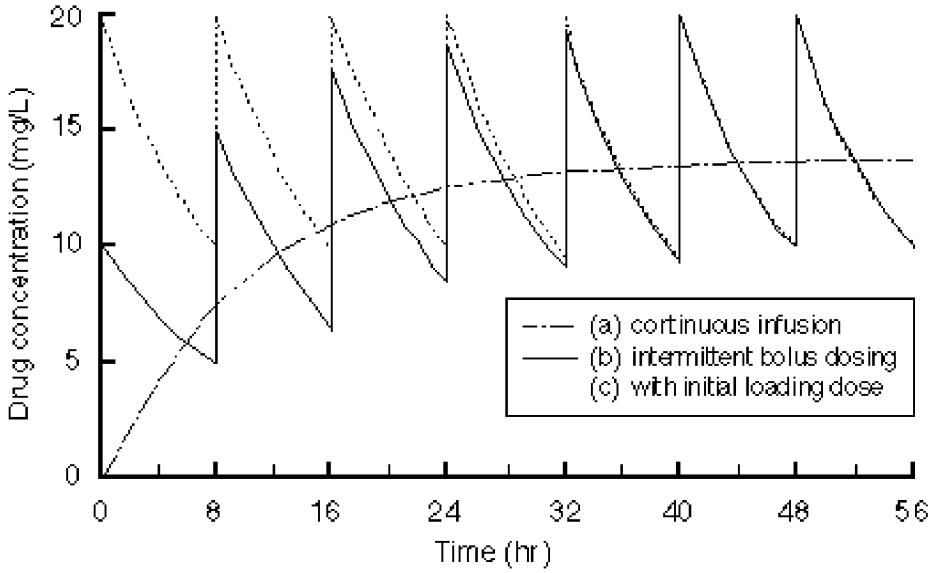
2. Use of a loading dose
The effect of a loading dose before an intravenous infusion has been discussed in Article 2 ('Volume of distribution' Aust Prescr 1988;11:36-7). The loading dose to achieve a desired concentration is determined by the volume of distribution (VD).

equation 2

Loading dose = desired concentration x V_D

Fig. 1	Intravenous infusion or intermittent dosing of a drug such as theophylline.	(a) Continuous intravenous infusion at a dose rate of 37.5mg/hour (b) Intermittent bolus dosing 300 mg 8-hourly (dose rate (dose/dosing interval) is 37.5 mg/hour)	Parameters used in the simulations were: CL = 2.6 L/hour, V_D = 30 L, $t_{1/2}$ = 8 hours. At steady state, the average plasma concentration over the dosing interval is the same as that during a continuous infusion (14.4 mg/L in this case). The therapeutic range for theophylline is 10-20 mg/L (55-110 mmol/L).

loading dose of 600 mg,
twice the maintenance dose



If the loading dose achieves a plasma drug concentration the same as the steady state concentration for the maintenance infusion (see equation 1), steady state will be immediately achieved and maintained. If the loading dose over- or under -shoots the steady state concentration, it will still take 3-5 half -lives to reach C_{ss} (see Article 2), but the initial concentration will be closer to the eventual steady state concentration.

With intermittent bolus dosing, Fig. 1 shows that where the dosing interval is equal to the half-life of the drug, a loading dose of twice the maintenance dose immediately achieves steady state. Half the loading dose (one maintenance dose) is eliminated in the first dosing interval (one half-life) and is then replaced by the first maintenance dose and so on.

The use of a bolus loading dose may sometimes cause problems if adverse effects occur because of the initial high plasma drug concentrations before redistribution occurs. This is the case for example with lignocaine, where CNS toxicity occurs if too high a loading dose is given too rapidly. In this situation, a loading infusion or series of loading infusions can be used to allow redistribution to occur while the loading dose is being given. (A common regimen for lignocaine is to give an initial intravenous dose of 1 mg/kg, followed by up to 3 additional bolus injections of 0.5 mg/kg every 8-10 minutes as necessary, and a maintenance infusion of 2 mg/minute.)

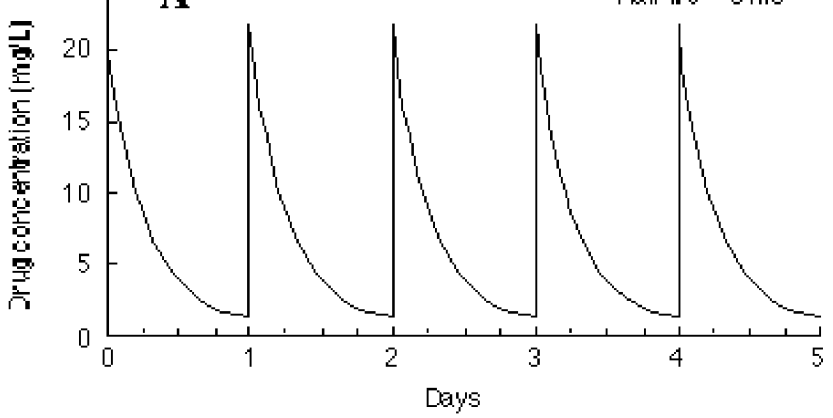
Another example is digoxin, where it is common for the loading dose to be divided into 3 parts given at 8-hourly intervals. Digoxin is slowly distributed to its site of action so the full effect of a dose is not seen for about 6 hours (see Article 2). Giving the loading dose in parts allows the full effect of each increment to be observed before the next is given so that potential toxicity can be avoided.

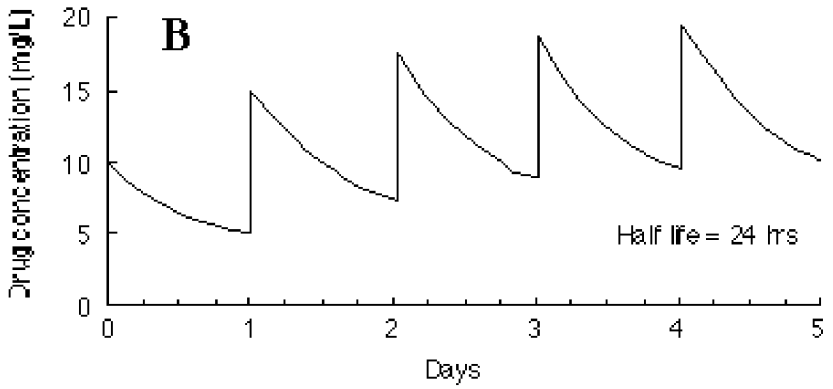
3. Effects of varying the dose interval

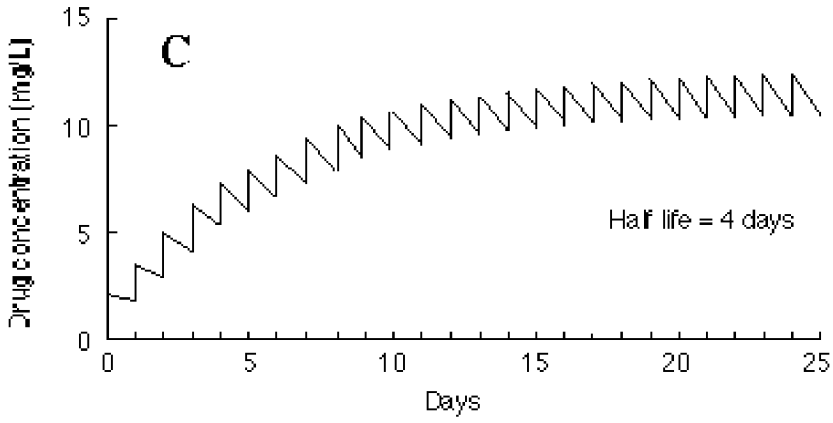
hours (characteristic of theophylline), the concentration is virtually at steady state shortly after the first dose, but there is a large fluctuation (94%) over the dosing interval ((C_{max} - C_{min}) divided by Cmax = 0.94). The drug with a half-life of 24 hours (characteristic of amitriptyline) takes 3-5 half-lives to reach steady state and the fluctuation over the dosing interval is 0.5. For the drug with a half-life of 96 hours (characteristic of phenobarbitone), it takes 12-20 days (3-5 half-lives) to reach steady state, and with once daily dosing (4 doses per half-life), the extent of fluctuation over the dosing interval is small ((C_{max} - C_{min}) divided by C_{max} = 0.16).

A dosing interval of about a half-life is appropriate for drugs with half-lives of approximately 8-24 hours allowing dosing once, twice or three times daily. It is usually not practicable to administer drugs with shorter half-lives more frequently. If such a drug has a large therapeutic index, so that a large degree of fluctuation over the dosing interval does not result in toxicity due to high peak concentrations (e.g. many antibiotics and beta-blocking drugs), it can be given at intervals longer than the half-life. For example, the plasma concentration time profile shown in Fig. 2A is similar to that for gentamicin when intravenous doses are given 8-hourly (half-life is 1-2 hours).

Fig. 2 Plasma concentration time profiles for drugs with half -lives of 6, 24 or 96 hours administered once daily	(A) Half-life is 6 hours (e.g. theophylline) (B) Half-life is 24 hours (e.g. amitriptyline) (C) Half-life is 96 hours (e.g. phenobarbitone)	See text for explanation.







By contrast, if the drug has a low therapeutic index and plasma concentrations need to be maintained in a narrow therapeutic range (e.g. theophylline with a therapeutic range of 10-20 mg/L (55-110 mmol/L)), use of a sustained release formulation will be necessary.

If the drug has a very long half-life (e.g. phenobarbitone with a half-life of 4 days), once daily administration may still be appropriate and convenient. The fluctuation over the dosing interval will be small, but it should be remembered that it will still take 3-5 half-lives (12-20 days in this example) to reach steady state. A loading dose could be used, but may not be feasible if tolerance to adverse effects occurs as the drug

activity) would be about 1.5 g - a lethal dose for a non-tolerant individual
(loading dose = C x V_D = 30 mg/L x 50 L).

Fig. 3

Effect of absorption rate and bioavailability on plasma concentration time profile. The example is characteristic of theophylline in children who metabolise the drug more quickly than adults. Note the effect of the sustained release preparation in reducing the degree of fluctuation over the dosing interval and allowing 12-hourly dosing for a drug with a short half-life and narrow therapeutic index (therapeutic range 10-20 mg/L (55-110 mmol/L)). The ka is the absorption rate constant (a measure of the rate of absorption in the same way that the elimination rate constant is a measure of rate of elimination).

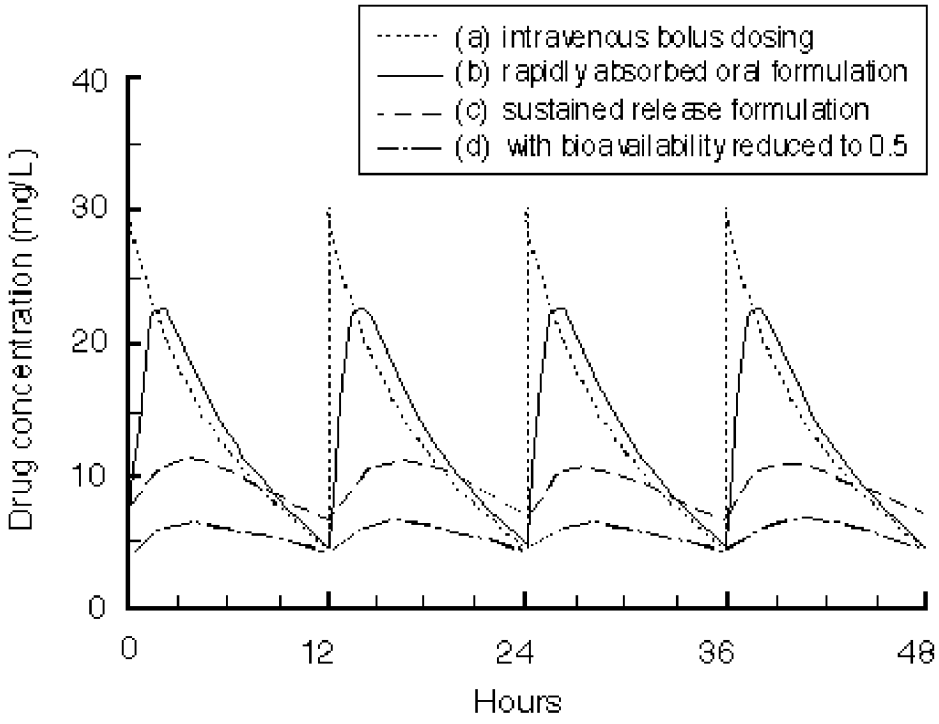
Parameters used in the simulations were:

Dose rate = 13 mg/kg/12 hours (1.08 mg/kg/hour),
V_D = 0.5 L/kg, $t_{1/2}$ = 4 hours, CL = 0.086 L/hour/kg,
F = 1

(a) instantaneous absorption (intravenous bolus dosing)
(b) ka = 1.5/hour similar to a rapidly absorbed oral formulation
(c) ka = 0.15/hour similar to a sustained release formulation
(d) as for (c) except that bioavailability (F) = 0.5

From equation 3:

for (a), (b) and (c), C_{ss} is 12.6 mg/L and
for (d), C_{ss} is 6.3 mg/L due to reduced bioavailability



4. Oral dosing

The principles applying to intermittent intravenous dosing also apply to oral dosing with two differences (Fig. 3):

the slower absorption of oral doses 'smooths' the plasma concentration profile so that fluctuation over the dosing interval is less than with intravenous bolus dosing. This smoothing effect is

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