Intravenous therapy is often required for acutely ill patients who are unable to take oral medicines and for drugs that have a low oral bioavailability. Most drugs are administered by bolus injection or short infusions but longer infusion times are sometimes necessary to reduce concentration-related adverse effects. Continuous infusions are often used to maintain therapeutic concentrations of drugs with short elimination half-lives.

**Intravenous bolus administration**

Mr B, a 72-year-old male patient, who weighs 80kg and has a serum creatinine concentration of 120mmol/L, is started on a gentamicin dose of 120mg three times daily to treat a severe infection caused by a gram-negative organism. “Peak” and “trough” blood samples are taken one and eight hours after the first dose and the gentamicin concentrations are found to be 5.0 and 1.8mg/L, respectively. Peak samples are important because response to gentamicin is concentration-dependent (see PJ, 31 July, p153).

Is 120mg eight-hourly an appropriate dosage regimen for Mr B?

Gentamicin is an aminoglycoside antibiotic used to treat potentially life-threatening infections. Response to therapy has been associated with achieving serum concentrations above 5mg/L, measured one hour after the dose (often called “peak” serum concentration), while trough concentrations with such doses are expected to be low (less than 2mg/L, a dosage interval of at least 9mg/L at one hour post dose concentration and a trough of 0.3 to 2.3mg/L). However, peak concentrations of only 3 to 5mg/L are recommended for streptococcal and enterococcal endocarditis. Trough concentrations greater than 2mg/L are associated with an increased risk of nephrotoxicity.

Some hospitals use “high dose, extended interval” gentamicin, where doses of 5 to 7mg/kg are given 24- to 48-hourly. Peak concentrations with such doses are expected to be well above 10mg/L and troughs are often below 0.5mg/L for at least four hours. Due to assay problems with these high and low concentrations, dose adjustment is often based on a gentamicin concentration measured between six and 14 hours after the dose.

To determine whether the dose is appropriate for Mr B, the peak (one hour post dose) and trough concentrations would be likely to achieve at steady state need to be calculated. It takes about five half lives for steady state to be achieved (see PJ, 19 June, p769). Mr B’s gentamicin elimination rate constant (k) and volume of distribution can be estimated from the concentrations that were measured after the first dose.

If a drug is administered as a single intravenous bolus dose, the concentration at any time (t) after the dose (Ct) is the maximum concentration (D–V; where D = dose and V = volume) multiplied by the fraction remaining at that time (exp–kt):

$$C_t = (D\div V) \times \exp^{-kt}$$

Where k, the elimination rate constant, is $Cl\div V$ ($Cl =$ clearance)

In Mr B’s case, the concentration measured eight hours after the dose (1.8mg/L) will depend on the proportion of the one-hour post dose concentration (5.0mg/L) that remains after another seven hours:

$$1.8 = 5.0 \times \exp^{-k \times 7}$$

$$\Rightarrow 0.360 = \exp^{-k \times 7}$$

By taking the natural log of both sides, the elimination rate constant (k) can be calculated:

$$\log_e 0.360 = –7k$$

$$\Rightarrow k = 0.146/h$$

Now we know k, Mr B’s volume of distribution can be calculated using one of the measured concentrations, for example, at one hour post dose:

$$5.0 = (120 \div V) \times \exp^{-0.146 \times 1}$$

$$\Rightarrow (120 \div V) \times 0.864$$

$$\Rightarrow V = 20.7L$$

Clearance can be calculated from:

$$Cl = kV = 3.0L/h$$

The measured concentrations suggest that the peak is too low although the trough is satisfactory. Mr B is to receive regular doses of gentamicin every eight hours. Concentrations will, therefore, accumulate until steady state is reached. To calculate the steady state concentrations, the extent of accumulation needs to be determined. The “accumulation factor” depends on the dosage interval (τ) and the elimination rate constant (k):

$$ Accumulation factor = 1÷ (1 – \exp^{-k\tau})$$

The full steady state equation for IV bolus administration, therefore, becomes:

$$C_{tss} = \frac{D}{V} \times \frac{\exp^{-kt\tau} \times 1}{1 – \exp^{-kt\tau}}$$

Mr B’s accumulation factor is 1.45 therefore his steady state concentrations will be:

$$C_{tss} = 5.0 \times 1.45 = 7.3 mg/L$$

$$C_{tss} = 1.8 \times 1.45 = 2.6 mg/L$$

The dosage regimen for Mr B is, therefore, not ideal; the steady state one hour post dose peak is below the target of >8mg/L and the trough is above the target of <2mg/L.

Figure 1 (p189) illustrates the accumulation to steady state and the predicted steady state profile of gentamicin concentrations in Mr B. The horizontal lines represent the minimum peak and maximum trough concentration targets.

**What should the dosage regimen be changed to?** If we aim for a concentration of around 9mg/L at one hour post dose and a trough of less than 2mg/L, a dosage interval of at least three elimination half-lives is required. This will allow the concentration to fall from 9 to 4.5 to 2.3 and then to 1.1mg/L. Four elimination half-lives would give a trough of 0.6mg/L. Because Mr B’s elimination half-life is 4.75 hours (0.693/0.146; see PJ, 19 June p769), the dosage interval should be at least 14
Mr B's dosage regimen should, therefore, be changed to 220mg daily, which should achieve a C₁hss of 9.5mg/L and a C₂₄hss of 0.3mg/L. Alternative options are 200mg daily (C₁hss of 8.6mg/L and a C₂₄hss of 0.3mg/L) or 240mg daily (C₁hss of 10.4mg/L and a C₂₄hss of 0.4mg/L).

**Intravenous infusion**

Ms M is a 25-year-old female patient, who weighs 60kg and has a long history of poorly controlled asthma. She is admitted to hospital with a severe asthmatic attack and is transferred to the intensive therapy unit for ventilation. It is decided to start treatment with theophylline and, because she has not received this drug previously, Ms M is loaded with a dose of 5mg/kg (300mg) aminophylline, which is administered intravenously over 20 minutes.

This aminophylline dose contains 237mg theophylline (300mg x 0.79; where 0.79 is the salt correction factor). Ms M is also started on an infusion of aminophylline at a rate of 500µg/kg/h (23.7mg/h of theophylline). After the infusion has continued for 24 hours, a sample is taken and the concentration measurement is 9.8mg/L (54µmol/L). The normal target serum concentration range for theophylline is 10 to 20mg/L (55 to 110µmol/L) although lower concentrations of 5 to 15mg/L (28 to 80µmol/L) may be adequate for some patients.

**Is this concentration likely to represent steady state?** The average elimination half-life of theophylline is around eight hours but is prolonged in patients who are receiving enzyme inhibitors, such as clarithromycin, and in patients with severe cardiac failure or hepatic cirrhosis. Assuming Ms M does not have any of these risk factors, 24 hours of therapy will cover three elimination half-lives and the concentration should, therefore, represent 87.5 per cent of the eventual steady state measurement. However, Ms M also received a loading dose and this will enable the concentration to get closer to the steady state value more quickly, as illustrated in Figure 2.

**A further theophylline concentration measurement taken at the end of the infusion was 10mg/L. If Ms M is to continue therapy with an oral liquid formulation of theophylline, what would be an appropriate dosage regimen?** Assuming a target concentration of 10mg/L, the daily dose can be determined in two ways. First, Ms M's theophylline clearance (Cl) can be estimated from the theophylline infusion rate divided by the measured serum concentration:

\[
Cl = \frac{23.7mg/h \div 10\ mg/L}{2.37L/h}
\]

The required dosing rate (in mg/day) is then 10mg/L x 2.37L/h x 24h = 569mg/day, assuming an oral bioavailability of 100 per cent

Alternatively, the dose rate can be determined by simply converting the hourly infusion rate to the amount administered in 24 hours, ie, 23.7mg/h x 24h = 569mg/day. The easiest option would then be a total daily dose of 540mg given as 180mg every eight hours, which should achieve an average steady concentration of 9.5mg/L (180/23.7 x 0.4mg/L).

It is often not possible to achieve a dose that is exactly the same when converting from intravenous to oral therapy and the nearest practical dose should therefore be used. This is rarely a problem since pharmacokinetic and drug assay variability mean that measured concentrations are often not the same as predicted concentrations anyway. The aim is to achieve dosage regimen that is likely to maintain concentrations within a range that is safe and effective for the individual.

**What would her steady-state theophylline concentration–time profile look like?** Because theophylline has a relatively short elimination half-life and the liquid formulation is absorbed quickly, it needs to be given three or four times daily to avoid excessive fluctuations in the profile that might otherwise lead to toxicity (high peaks) or loss of efficacy (low troughs). In common with intravenous bolus administration, the profile of drug concentrations during a dosage interval depends on V, Cl and the dosage interval. However,
The concentration at any time after a steady state oral administration will occur with regular dosing. In this case, however, an accumulation factor needs to be included for both absorption and elimination. The equation that describes the concentration at any time after a steady state oral dose is shown below:

\[ C_{ss} = \frac{D \times F \times k_a}{V (\frac{k}{k_a} - k)} \left[ \frac{\exp(-kt)}{1 - \exp(-k \tau)} \right] \]

Where \( F \) is the bioavailability, \( k \) is the elimination rate constant, and \( k_a \) is the absorption rate constant. Additional correction factors may be required if the drug is administered as a salt or concentrations are reported in molar units.

Ms M continues on oral therapy with theophylline liquid for a further three days then is changed to a controlled release theophylline preparation at a dose of 300mg twelve-hourly. This should achieve an average steady state concentration of 10.5mg/L.

Figure 3 illustrates the steady state profiles that would be obtained with the rapid release liquid formulation and the controlled release tablet formulation. It can be seen that the slow absorption phase flattens the profile, allowing the controlled release formulation to be given less frequently than the liquid formulation.

**Summary**

In addition to the pharmacokinetic characteristics of the patient, concentration-time profiles of drugs depend on the route of administration and on the input rate, which can be altered by the formulation. Individualisation of drug dosage regimens depends upon an understanding of the drug concentration-time profile that is best correlated with clinical response and a knowledge of how the drug is handled by the individual patient. Measurement of serum drug concentrations and appropriate interpretation of the results can help to ensure that patients receive optimal drug dosage regimens.

**Key for equations**

- \( C \) = concentration
- \( C_{ss} \) = steady state concentration
- \( C_t \) = concentration at any time (t) after the dose
- \( D \) = dose
- \( F \) = bioavailability
- \( k \) = elimination rate constant
- \( k_a \) = absorption rate constant
- \( \tau \) = dosage interval
- \( V \) = volume of distribution

**Further reading**


**Two portable showcases holding pharmacy items from the 19th and early 20th centuries are available on loan from the Royal Pharmaceutical Society’s museum for display at sites such as community pharmacies, hospitals, pharmaceutical companies, local museums, libraries, schools and other education centres.

One case is themed around the art of Victorian dispensing and includes a pill mortar, pill machine, pill rounders and slivers, powder folders and suppository moulds. The other case has a Victorian ceramic inhaler, a group of medicine and poison bottles, rectal ointment introducers and a range of 19th and early 20th century medicines.

Each case consists of a clear Perspex display unit on a waist-high plinth. The objects are permanently secured to the base of the sealed unit.
Practice points answers

1) If a drug is administered as a single intravenous bolus dose, the concentration at any time (t) after the dose (Ct) is the maximum concentration (D÷V; where D = dose and V = volume) multiplied by the fraction remaining at that time (exp^{-kt}): 

\[ Ct = \frac{D}{V} \times \exp^{-kt} \]

Where k, the elimination rate constant, is \( \frac{Cl}{V} \) (Cl = clearance).

Mr B’s estimated volume of distribution is 20.7 L and his elimination rate constant is 0.146/h.

So,

\[ C_{12h} = \frac{560}{20.7} \times \exp^{-0.146 \times 12} = 27.1 \text{mg/L} \times 0.173 = 4.7 \text{mg/L} \]

and

\[ C_{24h} = \frac{560}{20.7} \times \exp^{-0.146 \times 24} = 27.1 \text{mg/L} \times 0.03 = 0.8 \text{mg/L} \]

Plotting the 12 hour result of 4.7 mg/L on the Hartford nomogram suggests an adjusted dosage interval of 36 hours.

2) Ms M’s volume of distribution (V) can be assumed to be 28.8 L (0.48 L/kg x 60 kg — see PJ, 19 June, p769) and her clearance (Cl) is 2.37 L/h (Cl = infusion rate ÷ serum concentration, i.e., 23.7 mg/h ÷ 10 mg/L). Her elimination rate constant k (Cl ÷ V) will be 0.0823/h.

The dosage regimen is 300 mg 12-hourly.

Concentration at any time after a steady state oral dose is

\[ C_{ss} = \frac{FDk}{V(ka-k)} \left[ \frac{\exp^{-ht}}{1 - \exp^{-ht}} - \frac{\exp^{-kta}}{1 - \exp^{-kta}} \right] \]

For the liquid formulation,

\[ C_{12hss} = \frac{1 \times 300 \times 2.5}{28.8 \times (2.5 - 0.0823)} \left[ \frac{\exp^{-0.0823 \times 12}}{1 - \exp^{-0.0823 \times 12}} - \frac{\exp^{-2.5 \times 12}}{1 - \exp^{-2.5 \times 12}} \right] \]

\[ = \frac{750}{69.6} \times \left[ 0.372 - 0 \right] \frac{0.627}{1} \]

\[ = 6.39 \text{ mg/L (35.5 \( \mu \)mol/L)} \]

For the tablet formulation,

\[ C_{12hss} = \frac{1 \times 300 \times 0.22}{28.8 \times (0.22 - 0.0823)} \left[ \frac{\exp^{-0.0823 \times 12}}{1 - \exp^{-0.0823 \times 12}} - \frac{\exp^{-0.22 \times 12}}{1 - \exp^{-0.22 \times 12}} \right] \]

\[ = \frac{66}{3.96} \times \left[ 0.372 - 0.071 \right] \frac{0.627}{0.929} \]

\[ = 8.6 \text{ mg/L (47.7 \( \mu \)mol/L)} \]

3) \( C_{\text{average}} = \text{Dosing rate ÷ clearance} = \frac{FD \times (s \text{ m})}{Cl \times \tau} = \frac{1 \times 120 \times (1 \times 1)}{2.37 \times 6} = 8.4 \text{ mg/L (46.8 \( \mu \)mol/L)} \]

The Hartford nomogram for calculating gentamicin dosage intervals