Pharmacokinetics Made Easy…er

Association of Veterinary Anaesthetists
Spring 2010 Resident Training Day

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10.00 – 11.15  **Session 1: Introduction**
1. The relationship between pharmacodynamics and pharmacokinetics
2. The meaning of affinity, efficacy, potency, EC50, ED50, IC50, pA2
3. Antagonism, agonism and partial agonism
4. The implications of affinity and efficacy for whole animal responses
5. What happens after a single i.v. dose?
   a. plasma protein binding
   b. distribution
   c. elimination

11.15 – 11.30  **tea/coffee**
11.30 – 12.30  **Session 2: Quantifying the changes in concentration of drug in plasma after a single IV dose.**
1. single-compartment model
   a. half-time
   b. calculation of time required to reach a given concentration
2. clearance
3. volume of distribution
4. capacity-limited (zero order) elimination

12.30 – 13.15  **Lunch**
13.15 – 14.30  **Session 3: Changes in plasma concentration after a single extravascular dose: more complex models**
1. Absorption
2. Bioavailability

14.30 – 14.45  **tea/coffee**
14.45 – 16.00  **Session 4: Multiple doses and infusions.**
1. Steady state concentration
2. Maximum and minimum concentrations at steady state
3. Loading Doses
4. Infusions
1.1 Introduction

The relationship between pharmacokinetics and pharmacodynamics.

Pharmacokinetics deals with the absorption, distribution and elimination of drugs.

Pharmacodynamics includes the action of drug at its receptor (or ion channel or enzyme). The action of a drug is thought of in two stages: binding affinity and efficacy.

1.2 The meaning of... affinity, efficacy, potency, EC<sub>50</sub>, ED<sub>50</sub>, IC<sub>50</sub>, pA<sub>2</sub>

Affinity: “how well the drug binds.” “tightness of binding” The affinity determines the concentration of drug required to occupy the receptor. 
By definition: K<sub>i</sub> (the equilibrium dissociation constant) is the concentration required to occupy half the available receptors.
high affinity drug-receptor interaction: K<sub>i</sub> in the range nM to pM (10<sup>-9</sup> – 10<sup>-12</sup>M)
low affinity drug-receptor interaction: K<sub>i</sub> in the range mM to μM (10<sup>-3</sup> – 10<sup>-6</sup>M)

Efficacy: how well the drug activates the receptor. The extent to which the drug can induce the conformation change required for receptor activation and the extent to which signalling pathways are activated. Usually measured by determining the maximum response to a range of drugs and comparing them.
Antagonists have no efficacy.
Partial Agonists have less efficacy than a full agonist.

Potency is a combination of affinity and efficacy. It is usually measured as the concentration required for half the maximum response, that is, the EC<sub>50</sub>.

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**Binding is (generally) reversible** so two drugs can compete with each other for the same receptor. Can calculate concentrations required (if affinities are known).

### 1.3 Antagonism, agonism and partial agonism

**IC\textsubscript{50}:**
1. the concentration required to reduce the maximum response by half
2. is a reflection (but not an absolute measure) of the potency

K\textsubscript{d} is the affinity constant, measures potency

\( \text{pK}_d = -\log(K_d) \)

#### Antagonism

Sketch the responses for increasing concentrations of full agonist
1. alone
2. in the presence of a fixed concentration of an antagonist
3. in the presence of a higher fixed concentration of an antagonist

\( \text{pA}_2 = \text{negative log of the concentration required to shift the agonist } EC_{50} \text{ twofold.} \)
\( \text{pA}_2 = \text{pK}_d \text{ if antagonist is competitive and at equilibrium} \)

#### Partial Agonism.

Sketch the responses for increasing concentrations of full agonist
1. alone
2. in the presence of a fixed concentration of a partial agonist
Sketch the responses for increasing concentrations of a weak and a partial agonist in the presence of a fixed concentration of a full agonist at a just sub-maximal concentration.

Sketch the responses for increasing concentrations of a weak and a strong partial agonist in the presence of a fixed concentration of full agonist at its EC50 concentration.

1.4 The implications of affinity and efficacy for whole animal responses

Different tissues showed distinct degrees of signal amplification and thus the EC50 for a given agonist (eg isoprenaline) may be high in one tissue and low in another. Also, the extent to which a drug shows partial agonism can depend upon the tissue even though it is acting at the same receptors in both tissues.

- isoprenaline (full agonist)
- prenalterol (partial agonist)
1.5 Pharmacokinetics: What happens after a single I.V. dose?

1.5.a Binding to plasma proteins
such as albumin, β-globulin or acid glycoprotein can occur. Drug molecules exist in equilibrium between the free and protein-bound forms however it is only the free drug which is able to bind to its target protein and have a pharmacological effect. At the usual therapeutic doses the protein binding sites are not saturated so it doesn’t matter if you add two different drugs together – they are not going to exclude each other from binding. However there are a few examples that break this rule. Tolbutamide at normal therapeutic concentrations is quite close to saturation and so increasing the dose leads to a much bigger increase in free concentration than you might expect.

1.5.b Distribution into tissues.

structure of a cell membrane: the interior of the membrane is made up of lipids so highly charged drugs cannot diffuse through.

To get from the plasma into the tissues drugs have to cross cell membranes. The inside of the cell membrane is a lipid barrier and so only drugs which are sufficiently lipid soluble will be able to get across.
<table>
<thead>
<tr>
<th>chemical characteristic of drug</th>
<th>examples</th>
<th>areas it can access</th>
</tr>
</thead>
<tbody>
<tr>
<td>large</td>
<td>heparin</td>
<td>only in plasma</td>
</tr>
<tr>
<td>very polar (water soluble, fat</td>
<td>gentamicin</td>
<td>plasma + interstitial fluid</td>
</tr>
<tr>
<td>insoluble)</td>
<td>theophylline</td>
<td></td>
</tr>
<tr>
<td>moderately lipid soluble</td>
<td>ethanol</td>
<td>plasma + interstitial fluid + inside cells</td>
</tr>
<tr>
<td>very lipid soluble</td>
<td>morphine</td>
<td>concentrated inside cells</td>
</tr>
</tbody>
</table>

Some drugs such as heparin are too large to cross membranes and are thus confined to the plasma. Other drugs are very polar (water soluble and not lipid soluble) and thus don’t easily cross cell membranes – they can leak out of capillaries and get into the interstitial fluid (fluid surrounding cells) but can’t cross membranes into cells such as muscle or epithelial cells. Blood vessels surrounding the brain have special tight junctions which do not allow molecules to leak through. Thus only very lipid soluble drugs can enter the brain by diffusing through the cell membranes.

1.5.c Elimination.

**Definition** of Elimination: removal of the original drug from the bloodstream

*Either* by metabolism to a different chemical structure

*Or* by excretion usually in the kidney, but sometimes also in the breath or through the skin.

**Metabolism** occurs mostly in the liver but also in gut, lungs and plasma. It is usually a two-stage process, Phase I is an initial enzymatic modification by oxidation, hydrolysis, deamination, hydroxylation or dealkylation to give a derivative. Phase II takes this derivative which is then further modified by addition of a large water soluble group such as glucuronide. This makes it much more readily excreted in the urine.

Many of the Phase I reactions are carried out by one of the cytochrome P450 family of enzymes. There are a number of isoforms of cytochrome P450 – abbreviated CYP and a number. Some drugs show a preference for a particular isoform and sections of the population may have low or high levels of the enzyme which means that they metabolise particular drugs either very poorly or very rapidly.
Some examples of cytochrome P450 isoforms and their preferring drugs are:

**Isoenzyme P450** | **Drug(s)**  
--- | ---  
CYP1A2 | caffeine, paracetamol  
CYP2B6 | methadone  
CYP2C8 | paclitaxel  
CYP2C19 | omeprazole, phenytoin  
CYP2C9 | ibuprofen, warfarin  
CYP2D6 | codeine,  
CYP2E1 | alcohol, paracetamol  
CYP3A4, 5, 7 | ciclosporin

There are a number of **inhibitors of cytochrome P450** and this is an important mechanism for drug interactions. As well as drugs, dietary components such as grapefruit juice can inhibit cytochrome P450.

The levels of cytochrome P450 can be increased by a process known as **induction** where the presence of a particular drug or toxin causes increased gene transcription and production of more enzyme. Examples of such drugs/toxins are: St John’s wort, cigarette smoke, Brussels sprouts, some tranquilizers and anticonvulsants.

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Renal Elimination consists of three distinct processes:

1. **Filtration**: Blood is filtered at the glomerulus – all small molecules, which includes most drugs, end up in the filtrate (proteins are retained in the blood). Plasma protein binding decreases the amount of drug filtered.

2. **Reabsorption**: Nutrients etc are reabsorbed by active mechanisms (they don’t just diffuse across) back into the blood. Lipid soluble drugs are reabsorbed passively back into the blood. Waste products are not reabsorbed and remain in the urine.

3. **Secretion**: some drugs are actively transported (secreted) from the blood into the urine.

Reabsorption can be affected by pH if the drug is a weak acid or base and the unionised form can diffuse through membranes but the ionised form cannot.

\[ \text{HA} \rightleftharpoons A^- + H^+ \]

\[ pK_a = \log \left( \frac{[A^-]}{[HA]} \right) \]

\[ BH^+ \rightleftharpoons B + H^+ \]

\[ pK_a = \log \left( \frac{[B]}{[BH^+]} \right) \]

Calculate the effect of changing the pH from 7.4 to 6.5 on the proportion of charged and uncharged forms of buprenorphine which is a weak base with \( pK_a \sim 8.3 \).
Session 2. Single IV dose

2.1 Single compartment model.

In a single intravenous (i.v.) dose the drug is administered as a bolus and carried around the body in the blood. For the purposes of our calculations we can assume that the drug is instantaneously distributed throughout the plasma. In this model we are treating the whole of the plasma as though it’s fluid in a bucket and there is a constant flow of fluid into and out of the bucket. (You can imagine that fluid is constantly being absorbed from the gut and constantly being filtered into the urine in the kidney).

At time zero, the bolus of drug is introduced and immediately spreads throughout the bucket so that the concentration is uniform.

Questions:

Q: If \( D \) = dose, \( V \) = volume, \( C_0 \) = concentration at time of injection, what is the relationship between initial concentration, dose and volume?

Q: Say that we know that a drug is confined to the plasma and interstitial fluid and this volume corresponds to \( \sim 2 \) L, what dose would we need to achieve an initial concentration of 100 \( \mu g/ml \)?

Q: Say that we know that for a dose of 300 mg the initial concentration is 60 mg/L. What can we infer about the volume it is dissolved in?

Each minute a certain volume of plasma is washed out of the bucket. When the concentration in the bucket is high, each millilitre of urine will contain a lot of drug whereas when the concentration in the bucket is low each millilitre of urine will contain only a little drug. Putting this more formally, we say that the

rate of loss is proportional to the amount in body

rate of loss = \(-k_c \times \text{amount in body}\)

\[ k_c = \frac{\text{rate of loss}}{\text{amount in body}} = \text{fractional rate of drug removal} \]

For example: \( k_c = 0.1 \) h\(^{-1}\) means 10% loss per hour
This exponential decay is given by the equation where $k_e$ is the rate constant for elimination.

$$C = C_0 e^{-kt}$$

Knowing the half-time means that you can calculate how long the drug will last in the body. For example with the anabolic steroid nandrolone you could calculate how long one would need to wait in between the last dose and a drug test.

Q: If the plasma concentration is 3 $\mu g/L$, the half-time of the steroid is 10 days and the minimum concentration that the doping agency can detect is 0.04 $\mu g/L$ how long would you need between the last dose and the test?

Q: How long will pain relief from buprenorphine be likely to last after a single iv dose?

$D = 0.02$ mg/kg

$t_\circ = 6.13$ h $\Rightarrow k_e = 0.113$ h$^{-1}$

$V = 4.8$ L/kg (cat weighs ~ 5 kg)

minimal effective concentration ~ 2 ng/ml
2.2 Clearance

Clearance is the efficiency with which drug is removed from the body either by metabolism or renal elimination or both.

Clearance is the parameter which predicts the rate of elimination for a given plasma concentration.

\[
\text{rate of elimination} = \text{clearance} \times \text{plasma concentration}
\]

The overall clearance is the volume of plasma containing the total amount of the drug that is removed from the body in unit time. It has the units of flow rate. The total clearance is the sum of the hepatic clearance and the renal clearance (and clearance via any other routes of elimination).

It is quite straightforward to calculate the renal clearance because you can calculate the rate of elimination by measuring the amount of drug reaching the urine over a given time and then dividing that by the plasma concentration.

For example if 75% of drug reaching the liver gets metabolised and the blood flow to the liver is 90 litres/hour then the clearance of the drug by the liver is \(0.75 \times 90 = 67.5\) litres/hour.

Q: Clearance of lidocaine is halved by propranolol. Why? (Answer at the end)
Another example: if a drug is not metabolised and is not plasma protein bound and it is completely filtered at the glomerulus and not reabsorbed or secreted the clearance would be the same as the glomerular filtration rate, 125 ml/min in the average sized human.

If you don’t have an average-sized human you can relate the clearance of your drug of interest to the clearances of the following:

- creatinine and inulin have a renal clearance similar to the glomerular filtration rate
- para-aminohippuric acid is an excellent substrate for secretion so its extraction rate in the kidney is close to 1 and the clearance is close to renal plasma flow.

**Q: Taking a veterinary example – clearances of fleroxacin**


The excretion ratio of fleroxacin was measured in rabbits and dogs with and without probenecid (an inhibitor of active transporters involved in secretion of organic acids).

**excretion ratio = intrinsic renal clearance/glomerular filtration rate**

**Rabbits:**
- ~ 2 without probenecid
- ~ 0.68 with probenecid (blocks secretion)

**Dogs**
- ~ 0.60 both without and with probenecid

What can you conclude about the way in which renal clearance of fleroxacin occurs in dogs and rabbits?

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**Measuring plasma clearance.**

It is most common to calculate the plasma clearance using the area under the curve of the concentration vs time plot.

\[
CL = \frac{D}{AUC}
\]

*For a single-compartment model*, the AUC can be found from the initial concentration \(C_0\) and the rate constant for elimination \(k_e\).

\[
AUC = \frac{C_0}{k_e}
\]
Q: 500 mg dose of an antibiotic was given to each of two dogs one with impaired renal function. Estimate the half-time, clearance and volume of distribution.

<table>
<thead>
<tr>
<th>time (h)</th>
<th>patient 1</th>
<th>patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.0</td>
<td>14.7</td>
</tr>
<tr>
<td>2</td>
<td>16.1</td>
<td>11.9</td>
</tr>
<tr>
<td>3</td>
<td>15.2</td>
<td>9.7</td>
</tr>
<tr>
<td>4</td>
<td>14.4</td>
<td>7.9</td>
</tr>
<tr>
<td>8</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>5.9</td>
<td></td>
</tr>
</tbody>
</table>
2.3 Volume of Distribution.

Think back to our original simplest model where we reduced all of the blood plasma in the arteries, veins and capillaries into a single bucket. We said that when a dose of drug was added it distributed immediately throughout the volume. If we know the dose and the volume then we can predict the initial concentration.

Consider the other extreme where the drug has diffused into the tissues and is largely in the fat or bound to proteins inside cells. In this case the concentration in plasma will be very small when the amount in the body might be quite large. Since volume = mass/concentration, a small concentration means the apparent volume is quite large. If the drug is extensively sequestered in fat the volume of distribution can be very large, in fact it can be larger than the volume of the body.

The volume of distribution, $V_d$, is the volume of plasma that the drug would be dissolved in if it were all in the plasma. It is the apparent volume in which the drug is dissolved.

Values for $V_d$ are given as litres per kg body weight.

<table>
<thead>
<tr>
<th>Some reference values for $V_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>If a drug is confined to the plasma:</td>
</tr>
<tr>
<td>If a drug is confined to the extracellular space:</td>
</tr>
<tr>
<td>Restricted to body water: (able to readily cross cell membranes so inside and outside cells)</td>
</tr>
<tr>
<td>If a drug is extensively dissolved in fat or bound to protein in tissues:</td>
</tr>
</tbody>
</table>

In the very simplest “one-bucket” model where we have single exponential decay (which means the lnC vs t plot is a straight line) we said that the volume of fluid was constant. In this case the volume of distribution can just be calculated by:

$$V_d = \frac{D}{C_0}$$

where D is the dose and $C_0$ is the initial concentration before any of the dose has been eliminated.
In the more complex two-(or more) compartment model the initial volume of distribution might be only 3 – 12 L as the drug is just in the plasma and/or extracellular fluid. As it diffuses into tissues and gets sequestered there the apparent volume will become larger and can get up to 100’s or even 1000’s of litres. If repeated doses are given ultimately the system will reach a steady state and the volume of distribution will settle down to its “terminal phase” value.

If the data fits to a two-compartment model then the volume of distribution can be calculated from:

\[ V_z = \frac{CL}{k_z} \]

Where CL is the clearance and \( k_z \) is the terminal phase rate constant for elimination. The volume of distribution is now called \( V_z \) to indicate that it is the terminal phase volume of distribution.

A plot of concentration vs time for a two-compartment (two exponential) model appears to drop much more steeply (black circles) than a single exponential model (squares and dashed line). When plotted on a log scale (usually using natural logs) a single exponential decay shows a straight line whereas a two-exponential model has a curve at the lower time points.

**More than two compartments:**
Alfentanil, fentanyl and sufentanil require three exponential components to describe plasma concentration after a single iv dose

\[ C = C_1e^{-k_1t} + C_2e^{-k_2t} + C_3e^{-k_3t} \]
2.4 Capacity-limited (zero order elimination)

Some definitions:

**Flow-limited elimination = “first order” elimination:**
the rate of elimination is proportional to the concentration of drug in plasma.

**Capacity-limited elimination = “zero order” elimination:**
the rate of elimination is constant.

Usually first order elimination is observe at low(er) concentrations and zero order elimination at high(er) concentrations since capacity-limited elimination occurs when elimination mechanism is saturated.

Exceptions are drugs which spontaneously breakdown in plasma, eg atracurium.

Q: On the same axes sketch graphs of the relationship between the rate of elimination and the plasma concentration for first order and zero order elimination …

Q: On the same axes sketch graphs of the relationship between the plasma concentration and time after an i.v. dose for first order and zero order elimination.

Q: If you were to measure the clearance at a high concentration and a low concentration, would the values obtained be the same with zero order elimination? YES/NO; why?
3. Single Extravascular Dose

1. formulation and application
2. cross membrane
3. local blood flow
4. liver metabolism
5. systemic bloodstream
6. distribution into tissues to reach receptor/ion channel/transporter

**Oral Doses:**

- Intestine absorption across gut wall
- Portal vein
- Blood
- Metabolism in gut or gut wall
- **First-pass metabolism**
- Metabolism in liver

**Bioavailability** is the fraction of unchanged drug reaching the bloodstream

**Factors affecting absorption**

- too hydrophilic – can’t cross lipid membrane
- too lipophilic – not soluble enough
- acid or base – affected by pH
- substrate for transporter which pumps drugs back into gut

**Typical Bioavailabilities**

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular (im)</td>
<td>75-100%</td>
</tr>
<tr>
<td>Subcutaneous (sc)</td>
<td>75-100%</td>
</tr>
<tr>
<td>Oral (po)</td>
<td>1-100%</td>
</tr>
<tr>
<td>Rectal (pr)</td>
<td>30-100%</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5-100%</td>
</tr>
<tr>
<td>Transdermal</td>
<td>80-100%</td>
</tr>
</tbody>
</table>
Area under the curve = AUC

\[ availability = F = \frac{AUC_{oral}}{AUC_{iv}} \]

for equal doses

\[ availability = F = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{D_{iv}}{D_{oral}} \]

Rate of Absorption:

\[ t_{max}, C_{max} \]

time to peak
concentration at peak

determined by both rate constants of absorption and elimination
Rate of absorption can be modified by:
1- site of administration
2- drug formulation

\[ k_s = 0.04 \text{ h}^{-1} \text{ throughout} \]
\[ k_{\text{absorption}} \text{ varies:} \]
- \( 2 \text{ h}^{-1} \)
- \( 0.5 \text{ h}^{-1} \)
- \( 0.2 \text{ h}^{-1} \)
- \( 0.05 \text{ h}^{-1} \)

**Q:** The pH of human saliva is 5.4-7.5 whilst the pH of cat saliva is \( \sim 9 \). The pKa of buprenorphine is 8.3.

Sketch a graph of plasma concentration vs time for humans and cats highlighting the differences in \( t_{\text{max}} \), \( C_{\text{max}} \), and AUC. How might the pH of saliva affect the bioavailability of buprenorphine? (Data from Robertson et al (2005) J vet Pharmacol Therp 28, 453-460)

(Answer at end⁹)

**Q:** The antinociceptive effect of buprenorphine occurred at 90 min whilst the Cmax occurred at 30min. There was significant hysteresis in that the effect took also lasted for some time after the plasma concentration had dropped. Speculate as to why this might occur. (answer at end⁹)
**Q:** The kinetic profile of nicardipine was studied in six normal healthy male volunteers who received oral (40 mg) and intravenous (2 mg) nicardipine, first with water and second with grapefruit juice. Plasma concentrations were determined at regular intervals and the area under the concentration vs time plot was estimated. The results are shown in the table to the right.

<table>
<thead>
<tr>
<th>method of administration and dose (mg)</th>
<th>pre-treatment</th>
<th>nicardipine AUC (µg.ml⁻¹.min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v. dose = 2 mg</td>
<td>water</td>
<td>0.571</td>
</tr>
<tr>
<td>i.v. dose = 2 mg</td>
<td>grapefruit juice</td>
<td>0.565</td>
</tr>
<tr>
<td>oral dose = 40 mg</td>
<td>water</td>
<td>1.713</td>
</tr>
<tr>
<td>oral dose = 40 mg</td>
<td>grapefruit juice</td>
<td>3.412</td>
</tr>
</tbody>
</table>

Calculate the bioavailability of the oral dose with water and with grapefruit juice. Explain your results.

**Q:** Which of the following statements are correct?

A: All other parameters remaining unchanged, the slower the absorption process, the higher is the peak plasma concentration after a single oral dose.
B: After a single oral dose, an increase in bioavailability causes the peak time to shorten.
C: For a given subject, the AUC is proportional to the amount absorbed into the systemic circulation.
D: If \( k_{et} \ll k_a \), the terminal slope of the plasma concentration vs time graph reflects absorption not elimination.

*(Answers at end)*
**Q:** Procainamide can be administered orally as a conventional or slow release formulation. The following data were obtained (Graffner et al 1975 Clin Pharmacol Ther, 17, 414-423)

(a) Calculate the bioavailability for both oral formulations from both plasma and urine data.

(b) The half life of procainamide was 2.7h. Was the urine collected over a long enough time interval to obtain a good estimate of the cumulative amount excreted at infinite time?

(c) Calculate the renal clearance for the iv dose.

**answers at end***

### 4. Multiple Doses

#### 4.1 At steady state

\[ \tau_{ss} = 2 \text{ h} \]

A larger dose can be given over longer dose intervals but the concentration ranges much more widely.

**At steady state,**

\[
\text{the rate of entry to bloodstream} = \text{rate of elimination}
\]

The rate of entry to the bloodstream is the availability (F) multiplied by the dose rate (D/T). The rate of elimination is the clearance times the concentration as mentioned previously (under the definition for clearance).  

\[
\frac{D \times F}{T} = CL \times C_{ss}
\]

**Q:** IV morphine for dogs (10kg)

target concentration = 20 ng/ml  
\[ \tau_{ss} = 1.16 \text{ h} \]  
CL = 62.5 ml/min/kg = 625 ml/min  
Vd = 4.55 L/kg = 45.5 L  
What dose rate is required to maintain the target concentration?  
What dose is required for a dose interval of 2h?  
(Answer at end)

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4.2 Calculate the maximum and minimum concentrations at steady state.

In order to ensure that the plasma concentration is within a particular target range it is necessary to calculate the maximum and minimum concentrations at steady state.

Earlier we saw how to calculate the concentration after a particular time using equation 2.

\[ C = C_0 e^{-k_t} \]

Using \( t = T \) the dose interval, \( C = C_{\text{min}} \) and \( C_0 = C_{\text{max}} \) we have:

\[ C_{\text{min}} = C_{\text{max}} e^{-k_T} \]

Thus if we know the dose interval and the rate constant for elimination we can work out how big the jumps are between the maximum and minimum concentrations.

Imagine that the concentration has fallen over the dose interval from \( C_{\text{max}} \) to \( C_{\text{min}} \) how do we calculate the dose required to get back to \( C_{\text{max}} \) again? The jump in concentration from zero to \( C_0 \) is the same as the jump in concentration between \( C_{\text{min}} \) and \( C_{\text{max}} \) so we can write:

\[ C_{\text{max}} - C_{\text{min}} = \frac{D F}{V_d} \]

(We’ve written in the availability in case we want to use this to estimate the maximum and minimum concentrations after a rapidly absorbed oral dose).

For repeated doses, maximum and minimum concentrations (\( C_{\text{max}} \) and \( C_{\text{min}} \)) are obtained by solving these two equations together.

Q: Using the data for morphine iv doses in the previous question, calculate the maximum and minimum concentrations you’d expect with the suggested dose and dose interval. (Answer at end⁵)
Q: The plasma concentration of a new drug needs to be maintained between the therapeutic concentration of 2.2 µg/ml and the toxic concentration of 6.5 µg/ml.

Previous experiments determined the kinetic parameters:

\[ k_e = 0.12 \text{ h}^{-1}, \quad \text{CL} = 31.6 \text{ml/min}, \quad F \sim 1. \]

(a) What is the longest dose interval which will maintain the concentration between the toxic and therapeutic levels?

(b) What is the dose required at that dose interval?

(Answer at end)

### 4.3 Loading Doses

Loading dose is the dose required to reach \( C_{in} \) in the first dose interval. In the simplest “one-bucket” model this can be done in the same way as we did in activity 10 where we wanted to find the dose required to reach a given initial concentration. From equation 7:

\[
V_d = \frac{D}{C_0}
\]

If the volume of distribution is constant (ie the model is a single-compartment model and does not involve redistribution) then the ratio of the maintenance dose to the initial concentration will be the same as the ratio of the loading dose (LD) to the desired concentration.

\[
V_d = \frac{D}{C_0} = \frac{LD}{C_{av,ss}}
\]

rearranging:

\[
LD = V_d \times C_{av,ss}
\]
Q: An antibiotic is given i.v. and the pharmacokinetic parameters were determined:
\[ k_e = 0.073 \text{h}^{-1}, \ AUC = 5916 \ \mu\text{g.ml}^{-1}.\text{min}, \ CL = 14.8 \text{ ml/min}, \ V_d = 12.2 \text{ L} \]

(a) Assuming single exponential elimination, if a single i.v. dose of 25 mg is given what would the initial concentration \( C_0 \) be?
(b) If an i.v. dose of 25 mg is given every 6 h, what would the steady state concentration be?
(c) What would the loading dose be to get steady state concentration in the first dose interval?

(Answer at end)

4.4 Infusions

The equation for the concentration as a function of time after the beginning of an infusion is.

\[ C_p = C_{ss} \left( 1 - e^{-k_e t} \right) \]

This represents the smooth line in the figure opposite.

You can combine this with the equation

\[ R_0 = CL \times C_{ss} \]

where \( R_0 \) is the infusion rate (note the similarity between this equation and the previous one where \( R_0 \) is replaced with \( DF/T \)) to get:

\[ C_p = \frac{R_0}{CL} \left( 1 - e^{-k_e t} \right) \]

We can use this equation to determine the time required to reach a particular concentration or a particular proportion of the steady state concentration (usually 0.9).
Q: In a previous exercise we saw that the plasma concentration of a new drug needs to be maintained between the therapeutic concentration of 2.2 μg/ml and the toxic concentration of 6.5 μg/ml. Previous experiments determined the kinetic parameters:
k_c = 0.12 h^{-1}, \text{CL} = 31.6 \text{ml/min}, F \sim 1.

If the dose was 68mg and the dose interval 9 h how long after the first dose was administered would it take to reach the therapeutic concentration of 2.2 μg/ml?

\[
C_p = \frac{DF}{CL \cdot T} \left(1 - e^{-k_c t}\right)
\]

\[
2.2 \mu g / ml = \frac{68000 \mu g}{31.6 \text{ml} / \text{min} \times 9 \times 60 \text{min}} \left(1 - e^{-0.12 t}\right)
\]

\[
0.552 = \left(1 - e^{-0.12 t}\right)
\]

\[
e^{-0.12 t} = 0.448
\]

\[-0.12t = -0.803\]

\[t = 6.7h\]

Q: Given the equation

\[C_p = C_{ss} \left(1 - e^{-k_c t}\right)\]

derive an expression for the time required to reach 90% of steady state concentration.

\[
\frac{C_p}{C_{ss}} = 0.9 = 1 - e^{-k_c t}
\]

\[e^{-k_c t} = 0.1\]

\[-k_c t = -2.303\]

\[t = \frac{2.3}{k_c}\]

This demonstrates that the only parameter that determines the time to reach 90% of the steady state concentration is the rate constant for elimination.
Q: Draw a graph of plasma concentration vs time for a series of curves where the (a) rate of infusion increases (b) the rate constant for elimination increases.

Infusions with capacity-limited elimination

![Graph of plasma concentration vs time for normal and saturating kinetics.](image)
Q: You have a new candidate drug for a neurological disorder. The drug was given by infusion - data for Cp shown in table.

<table>
<thead>
<tr>
<th>time (h)</th>
<th>$C_p$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R_0 = 60$</td>
</tr>
<tr>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>1.5</td>
<td>4.3</td>
</tr>
<tr>
<td>2</td>
<td>4.6</td>
</tr>
<tr>
<td>2.5</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
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<tr>
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<tr>
<td>6</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>0.0</td>
</tr>
<tr>
<td>8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

(a) For $R_0 = 60$ µmol/h, calculate the half-life, clearance and volume of distribution.
(b) Given the pharmacokinetic parameters you've calculated, comment on the drug's suitability for use in a neurological condition (where the drug must cross the blood brain barrier).
(c) How does the response differ between the higher and lower infusion rates? Suggest reasons for the difference.
(d) The effective concentration is 10 µmol/L. Would either of these infusion rates be appropriate? If not, calculate an appropriate infusion rate to reach the effective concentration.

answers at end

Q: Which one or more of the following statements is correct? (answers at end)
A: The time to reach a plateau concentration depends on the rate of infusion
B: All drugs having the same clearance reach the same plateau concentration when given at the same iv infusion rate.
C: Drugs with the same clearance generally reach the plateau concentration at the same time.
Some Answers to Questions where not indicated in the text.

a Reduction in cardiac output and decreased hepatic blood flow
b Shiba et al suggested that floxacain was excreted into urine by both glomerular filtration and renal tubular secretion in rabbits, but only by glomerular filtration in dogs. In both cases there was some passive reabsorption.
c The bioavailability of buprenorphine via oral transmucosal administration was 30-50% for humans and ~100% for cats.
d There may be a barrier to access of drug to its active site – either the blood brain barrier or diffusion through tissues. Alternatively the onset of binding to the receptor is slow and the dissociation is also slow – the receptor has high affinity for buprenorphine.
A: incorrect – peak would be lower
B: incorrect – bioavailability has no effect on peak time
C: correct if clearance is constant
D: correct

(a) F (conventional oral dose from plasma AUC) = 20.9/13.1 x 500/1000 = 0.8
   F (conventional oral dose from urine data) = 586/332 x 500/1000 = 0.88
   F (slow release from plasma AUC) = 19.9/13.1 x 500/1000 = 0.76
   F (slow release from urine data) = 554/332 x 500/1000 = 0.83

(b) Yes – 48 h would be 18 half-lives.
(c) fraction unchanged for conventional oral dose is 332/500 = 0.66
   total clearance for iv = D/AUC = 500mg / 13.1 mg.h/L = 38.2 L/h
   renal clearance = 0.66 x 38.2 L/h = 25.2 L/h

\[
\frac{D}{T} = 625ml \text{ min}^{-1} \times 20ng / ml
\]
\[
\# \frac{D}{T} = 12500ng / min \times 0.75mg / h
\]
\[
D = 0.75mg / h \times 2h = 1.5mg
\]

\[ C_{\text{min}} = 14ng/ml; C_{\text{max}} = 47 ng/ml \]
\[ T = 9h, D = 68mg \]

(a) The initial concentration is 2.05 µg/ml
(b) The average steady state concentration is 4.69 µg/ml.
(c) The loading dose required to reach a concentration of 4.69 µg/ml in the first dose interval is 57 mg.

K (a) CL=12.2 L/h; Vd = 9.3L
(b) The volume of distribution is quite small indicating that the drug is confined to the plasma and interstitial fluid. This suggests that it doesn’t cross membranes readily and thus might not be suitable for a condition where it is essential for the drug to cross the blood brain barrier.
(c) The response for the higher infusion rates gives plasma concentrations that are more than 500/60 times the lower plasma concentrations. This suggests that the elimination may be zero order at higher concentrations. Possibly the enzyme metabolising the drug is saturated at the higher infusion rate.
(d) The lower infusion rate would not be appropriate as the highest concentration is below this level. The higher infusion rate would also not be appropriate as it would not reach steady state. A possible infusion rate might be: \[ R_0 = CL \times C_{av} = 12.24L / h \times 10 \mu mol / L^{-1} = 122.4 \mu mol / h \]

\[ ^1 \text{ A incorrect} \]
\[ ^2 \text{ B: correct} \]
\[ ^3 \text{ C: only if Vd’s are the same} \]