PHARMACOLOGY

"The dose of everything is one, four times a day"

A drug can be defined as a substance given to patients in the expectation of benefit. Drugs produce their effects by affecting a specific target or targets. Drug action may occur at:

- Sites vulnerable to the direct physical
- Sites vulnerable to chemical action of drugs
- At receptor sites
- Enzyme sites

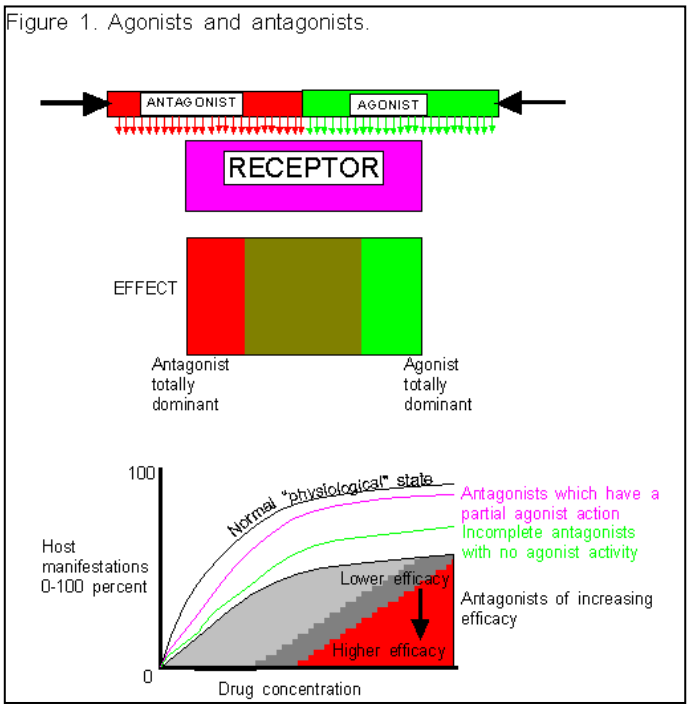
Drugs may produce effects at more than one site.

Action on sites vulnerable to physical effects of the drug
Bulk or irritant purgatives act in this way.
Action on sites vulnerable to chemical effects of the drug
Local or general anaesthetics act in this way.

Actions with receptor sites

A receptor is a specific tissue protein which binds specific substances (Fig. 1). An *agonist* combines with a receptor to produce a response. An *antagonist* combines with, partially or completely, a receptor to prevent an agonist (usually a natural bodily messenger substance) from producing its usual effect. An antagonist drug is termed a *partial agonist* if it, in combining with the receptor, produces an effect similar but less than that of the agonist agent

Figure 1. Agonists and antagonists.



With receptor site mechanisms the effect on bodily function depends:

- On the action produced by the receptors
- On the ease of occupation "saturation" of receptor sites with the drug
- The reversibility of such occupation
- Whether the drug occupies all receptor sites

If drug-receptor binding is slowly reversible then the drug is said to be potent, even if the extent of the effect is small. It is thus possible to have a drug of high potency but with little effect.

Action with target enzymes

Most drugs acting in this way usually inhibit rather then enhance enzyme action.

Drug absorption

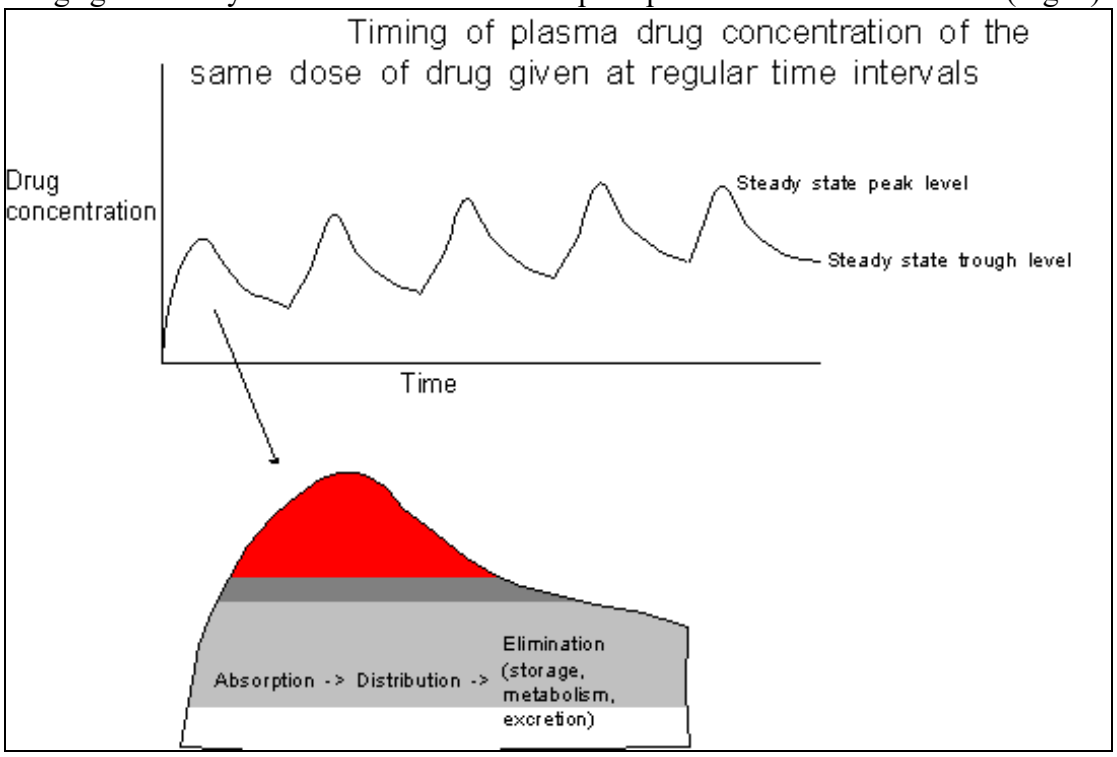
In general:

- Orally administered drugs are usually absorbed by the upper small gut
- Cell membranes let lipid soluble drugs through rapidly thus:

  Lipid soluble drugs tend to be rapidly and/or completely absorbed

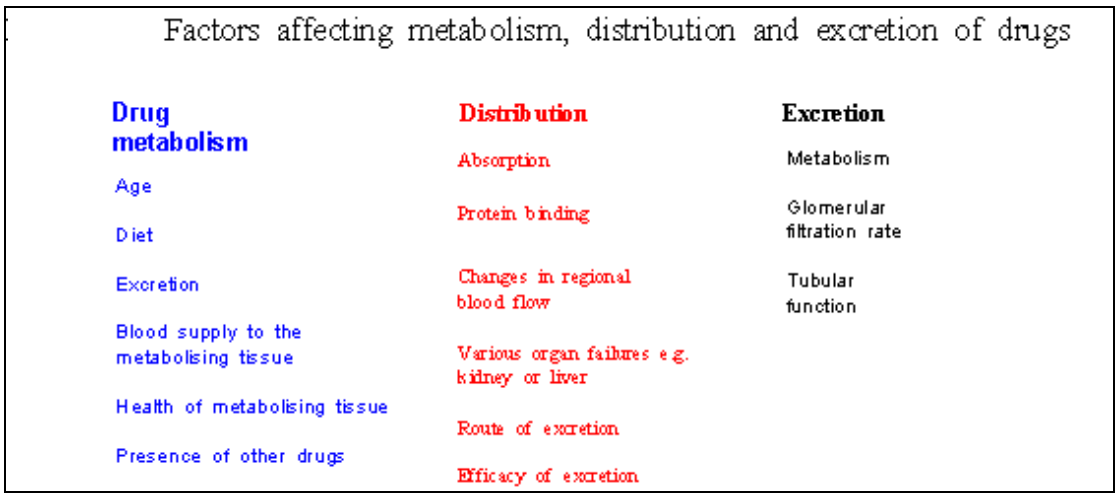
  Water soluble drugs tend to be absorbed more slowly and/or incompletely absorbed
- Absorption of lipid soluble drugs tends to be enhanced by food
- Water soluble drugs are better absorbed on an empty stomach

Drugs given orally are often show a "hill-shaped" plasma concentration curve (Fig. 2).



Drug distribution depends upon:

- The size of the dose
- The route of administration
- The rate of administration
- Ability of the body to distribute the drug
- Drug binding to plasma proteins
- Metabolism characteristics
- Excretion characteristics



Drug metabolism

In general lipid soluble drugs are metabolized, mostly in the liver, to water soluble compounds prior to excretion in the bile or urine. Mechanisms include:

- *Oxygenation* in the liver using system such as cytochrome P450 enzymes (if the liver is failing oxidation tends to be less effective)
- *Conjugation* in the liver with compounds such as glucuronic acid to produce (mostly) inert compounds. Large conjugates tend to be excreted in the bile whilst small conjugates tend to be excreted into the urine. Conjugation is often rate limited (however if the liver is failing combination with glucuronic acid tends to remain effective)
- *Acetylation* in the liver. Individuals tend to vary in the rate at which this can occur: there are fast acetylators and slow acetylators

Drug excretion

Most drugs and their metabolites are excreted into the bile or into the urine. The rate of elimination depends upon:

- The drug binding to plasma proteins
- The plasma concentration
- The molecular size
- The functional integrity of the liver and/or kidney

The peak and trough nature of drug levels in the plasma and how each part of the curve reflects absorption, distribution or elimination.

First order elimination occurs when a constant proportion of the drug is eliminated (by metabolism and/or excretion) in unit time. First order elimination is not to be confused with first pass metabolism. First pass metabolism is said to occur when most, if not all, of the drug is metabolized during its first passage through a metabolizing organ (usually the liver).

Drug clearance

Drug clearance is the volume of plasma cleared of the drug in unit time and this reflects the combined result of the drug's metabolism and excretion. Rapid clearance is usually associated with rapidly declining drug action. However some drugs with high rates of clearance from the plasma may be metabolized to a related compound that has more effect than the originally administered drug.

With some drugs increasing concentrations are mirrored by increasing metabolism. Similarly with some drugs increasing concentrations are mirrored by increased excretion. Saturation metabolism (with risks of toxicity) occurs when the body has only a limited metabolic breakdown ability for drugs (including phenytoin and alcohol). Thus clearance (and thus concentration) of drugs which exhibit saturation metabolism may vary widely depending upon circumstances.

Bioavailability

Bioavailability is defined as the proportion of the drug reaching the systemic circulation and depends on the extent of absorption and the extent and mode of clearance. Drugs given intravenously are thus initially 100 percent bioavailable and thus intravenous administration is the "gold standard" against which other routes of administration (oral, intramuscular, subcutaneous etc.) must be judged. A drug can have a separate bioavailability profile for each route of administration.

Most drugs which are not given intravenously have less than 100 percent bioavailability because their availability is diminished before they reach the systemic circulation because of:

- Incomplete absorption (usually by the gut)
- Digestion or metabolism in the gut
- Metabolism (usually in the liver but occasionally elsewhere)
- Rapid excretion

Figure 4a and 4b shows drug levels obtained if a drug is given intravenously and a constant *proportion* is eliminated over time and also the levels obtained if the elimination rate is limited to a constant *quantity* in unit time. The time necessary for a drug concentration to halve is known as the half-life. The half life does *not* mean time to half the effect but rather is a measure that enables prediction of risk of accumulation, time taken to achieve maximum concentration after multiple doses and decay in concentration after drug stoppage.

Figure 4a. Serum drug levels obtained if a drug is given intravenously and a constant *proportion* is eliminated over time.

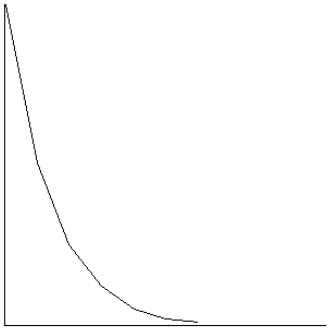
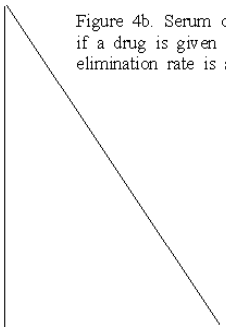


Figure 4b. Serum drug levels obtained if a drug is given intravenously and the elimination rate is a constant quantity in unit time



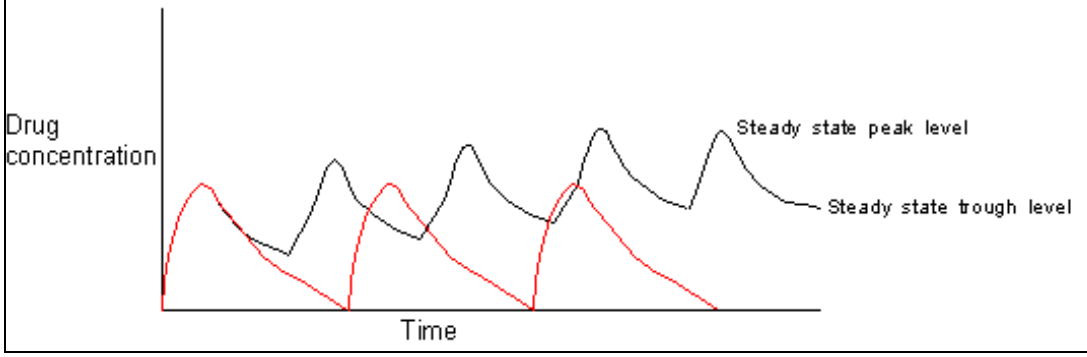
Drug accumulation

Drugs given on a regular basis may accumulate (depending on the dose, frequency of administration, and the drug half life). Usually a steady state will be reached (unless there is saturation metabolism or saturated excretory ability). If the interval of dosing is the half life then it takes about five half lives before a steady state is achieved (Fig. 5).

Figure 5. Timing of plasma drug concentration of the same dose of drug given at regular time intervals

— = at intervals of less than one half life

— = at intervals greater than one half life



If the rate of elimination is directly proportional to the concentration then fifty percent of this steady state concentration will be reached after one half-life, and 75 percent after two half-lives. Thus if "instant achievement" of a steady state concentration is required then initial intravenous administration is usually required (or administration of a drug with rapid and complete absorption) with an initial loading dose higher than

routine doses. If the dosing interval is less than the half life it still takes about five half-lives for a steady state to be achieved but there will be less fluctuation in concentration (see Fig. 2). If the interval of dosing is more than the half life then there will be no steady state but peaks and troughs will be more obvious. As an approximation peak levels reflect drug activity, and trough levels reflect the tendency for accumulation. If a drug (such as heparin) has a short half-life then it has to be given by continuous infusion or in a slow release form.

The longer the half-life the longer the interval can be between doses. The concentration of drugs with first order elimination is, at steady state level, directly proportional to the dose absorbed and inversely proportional to the clearance. *Drug effects of course may not bear a relationship to the plasma concentration.*

Protein binding

The total (free + protein bound) plasma concentrations of drugs are often measured but in general it is the *free* unbound portion that exerts effects. The effect of protein binding depends on the proportion of the drug that is bound and the tenacity with which it is bound. The plasma concentration may be low if any free drug is rapidly bound to receptors or disappears rapidly into cells. Thus a drug might be highly effective despite having low free plasma levels.

Routes of drug administration

Enteral means via the gastrointestinal tract and parenteral means by other routes, usually meaning by intravenous or intramuscular injection.

Drugs that are swallowed (tablets, capsules, liquids, delayed or targeted release formulations) are preferred by most people. Swallowed drugs, if removed by first pass metabolism by gut or liver, are less available to exert their effect.

Sublingual or buccal administration avoids first pass metabolism as drugs are absorbed into veins which drain directly to the heart (and not via the liver), the effect can be rapid, the preparation can be spat out once the desired effect occurs, and can be used if patients are vomiting or if gut absorption may be unpredictable.

Suppositories are useful if patients are vomiting and can be an alternative for children if they reject oral or injection routes. Because a proportion of blood from the large gut may drain directly to the liver some drugs may undergo first pass deactivation.

Intravenous administration guarantees that the drug is circulated in the body's distribution system even if the patient is hypotensive (when absorption by other routes may be impaired). If a drug is given intravenously then the concentration in plasma usually declines exponentially. Giving drugs intravenously as a bolus causes high, often transitory, peak levels especially if given in less than the circulation time. If bolus peak levels are too high then drugs can be given by infusion (perhaps with an

initial loading dose). Intravenous drugs can be discontinued instantly, although the effects may take some time to resolve. Some drugs cause small veins to become inflamed and such drugs may have to be given into large veins near the heart (using "central" rather than "peripheral" lines).

Intra-arterial administration is usually reserved for targeted delivery of anti-cancer drugs to areas supplied by accessible single arteries.

Intramuscular administration is painful and therefore disliked by patients. Absorption is variable in timing and extent. The volume of drug that can be injected is limited and intramuscular administration is contraindicated in patients with a tendency to bleed. Depot preparations given every few weeks may be very useful particularly if poor compliance with other routes of administration is anticipated.

Intravaginal administration can be used to treat vaginal pathologies.

Subcutaneous or intracutaneous administration is relatively pain-free and is simple and is safe for patients to give themselves (e.g. insulin for diabetics).

Topical administration is useful for skin conditions. A high concentration of the drug can be given directly onto the affected area. Sensitization to the drug may occur but systemic absorption is usually minimal.

Transdermal administration is possible if topical drugs are systemically absorbed but there may be variation in absorption. Glyceryl trinitrate, oestrogens and some painkillers can be administered in cutaneous patch form.

Inhaled drugs (given as aerosols, dry powder, or nebulized) are useful for treatment of lung problems (notably asthma). Only a proportion actually reaches the periphery of the lung and the amount depends at least in part on the technique of the patient, the particle size and the speed at which it is delivered.

Targeted release drugs are usually given orally with planned release at relevant levels of the gut. Targeted release drugs are very useful if the release at the appropriate site can be guaranteed.

Prodrug administration entails the giving of an inactive compound which when metabolised releases the active drug. This technique is used (very eloquently) when acyclovir is used for *Herpes simplex* infection. Only the infected cells are able to metabolise aciclovir to its active constituent by using a *Herpes simplex* specified enzyme, and the destruction of the prodrug inside the infected cell causes a low intracellular concentration of the prodrug so that the virus inside the cells draws even more of their destroyer into the infected cells along a diffusion gradient.

Adverse drug reactions

There are two main varieties of adverse drug reactions.

Dose-dependent reactions which are usually predictable and which produce unwanted accentuations of desired effects or unwanted occurrences of known side effects. Such reactions may be related to an individual patient's absorption, distribution, metabolism or excretion of a drug. Drugs causing dose-dependent side effects could, if appropriate, be recommenced later but at a lower dose.

Idiosyncratic reactions are unpredictable, are usually not dose-dependent and are usually caused by immune-mediated or "allergic" mechanisms. With idiosyncratic reactions the drug often has to be stopped and not used again. However if the reactions are mild (e.g. a trivial skin rash) and the drug has a short half-life then it may be reasonable to continue the drug and the reaction may settle. Desensitization can be undertaken if administration of a particular drug is essential.

Drugs given in pregnancy or to breastfeeding mothers may have adverse effects because foetal tissue is particularly vulnerable.

Drug interactions

Drug interactions may occur if two or more drugs are given simultaneously. Often such drugs have similar absorption, metabolism, excretions, effects or side effects.

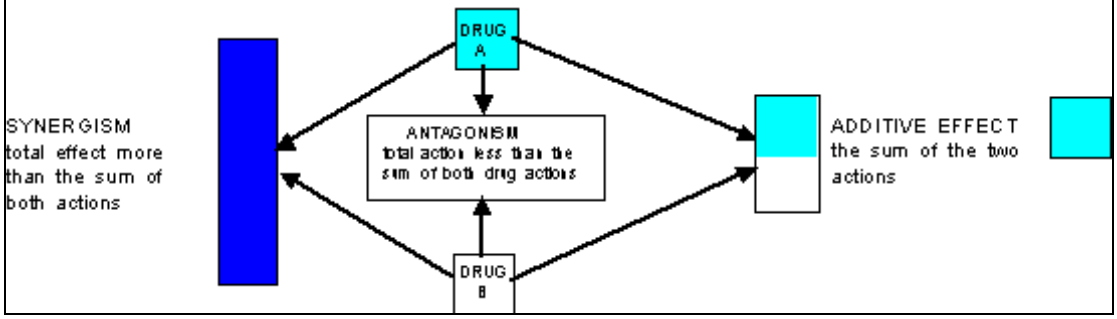
In general the greater the number of drugs prescribed the greater the chance of interactions, and the greater the chance that it will be difficult to identify the causative drug.

Drug interactions may occur:

- In syringes or intravenous giving sets
- In the bloodstream
- In the gut
- By one drug boosting or inhibiting enzymes that metabolise another drug
- By one drug affecting extent or tenacity of protein binding of another drug
- By competition for metabolism or excretion
- By affecting cell transport mechanisms
- At receptor sites

Interactions may cause *additive* effects if the superficial actions of the two drugs remain independent (Fig. 6).

Figure 6. Drug interactions. Additive, synergistic, and antagonistic drug interactions.

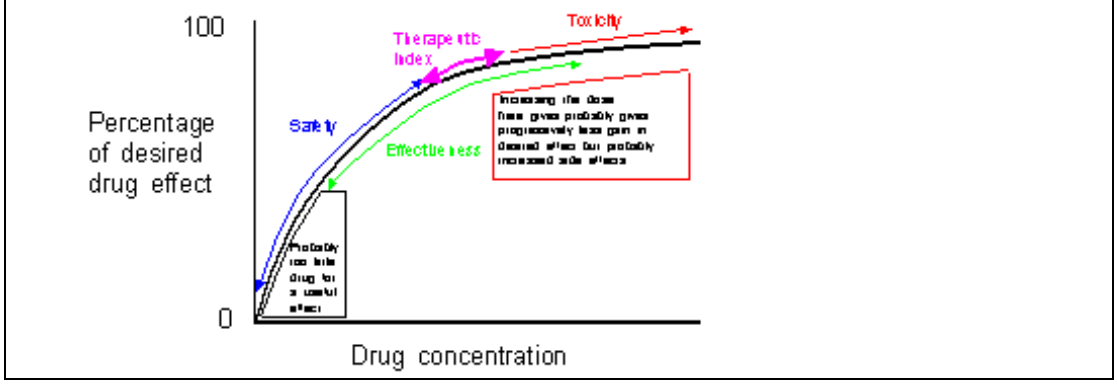


However there may be significant extra advantages other than "addition of actions" when the two are given together. For example with two antibiotics there might well be a reduction in the chance of resistance to either drug developing. With *synergistic* interactions the effect of the combination is greater than the sum of the actions of each contributor. With *antagonistic* interactions the result of the combination in less than the sum of the actions of each contributor.

Therapeutic index (Figure 7)

Drugs are said to have a narrow therapeutic index if there is a small margin between safety and toxicity.

Figure 7. Relationship between drug concentration and likely effect



Drugs with a wide therapeutic index (a wide margin between safety and toxicity) are safer. Such drugs often act on mechanisms not present in humans. For example penicillins and cephalosporins act against bacterial cell walls and, because humans have different cell walls, these antibiotics can be given in doses which are highly toxic to bacterial but not human cell walls.

Measurement of drugs

With a few important exceptions measurement of plasma levels is a substitute for what is really important to know - the target organ concentration of the drug. Plasma levels of the drug are important:

- When they affect the blood itself e.g. anticoagulants
- To ensure effective levels (usually peak levels are important)
- To prevent accumulation (usually trough levels are important)

- To detect toxicity and overdoses
- To decide on treatments for overdoses
- To detect non-compliance
- To make dosage adjustments (especially if there is failure of metabolizing or excreting organs)
- To assess drug interactions

Compliance

In practice there are several interventions that help patients take their drugs. Whenever appropriate:

- Prescribe the minimum number of drugs
- Reduce the frequency of drug dosage
- Increase dosage by increasing tablet strength
- Indicate why the drug(s) is being given
- Tell the patient when to take the drug
- Anticipate poor recall of instructions by the patient and write down the key instructions
- Warn the patient of significant side effects

Clinical responses to treatment

A graded response is one in which a continuously changing drug concentration (usually meaning plasma concentration) causes a continuously changing clinical response. Such responses may be reversible or non-reversible. In practice at low drug concentrations such responses are usually directly proportional to the concentration. At concentrations between about 20-80 percent of the maximum effective dose the response is proportional to the logarithm of the concentration, and at higher concentrations changes in concentration have relatively little therapeutic effect (but often toxic effects). Some other drugs, in contrast, have an all or none response.

The intensity of effect is related to:

- Dose
- Route of administration
- Rate and efficacy of clearance
- Activity of drug metabolites
- Time taken to penetrate tissues
- Extent of penetration into tissues
- Tolerance to the drug
- Other drugs being given

Drug dosing

Somewhat counterintuitively, doubled doses of some drugs may only prolong the *duration* of drug concentration slightly. Thus in general more frequent administration of smaller doses is more useful than less frequent administration of higher doses. The less frequent high doses would cause higher peak levels (possibly with increased therapeutic effect but possibly increased toxicity) but lower trough levels. Be aware that three times a day to a patient does not necessarily mean 8 hrly and four times a day does not necessarily mean 6 hrly.