Adjusting therapeutic dosage regimens to optimise the balance of benefit to harm

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What is a therapeutic dosage regimen?

A dosage regimen usually consists of a series of doses, given at specified intervals by a specified route of administration and for a specified duration.

Several principles dictate the choice of drug:

- *Whether drug therapy is necessary*: always seek good evidence that drug therapy affects clinically important end-points. If you decide to give a drug to a patient who has a disease or is taking another drug that might change the effects of your therapy, consult the British National Formulary for advice on using (or not using) that drug in those circumstances.
- *Whether there are specific indications for a particular drug*: for example, in a patient with hypertension and diabetes mellitus, an angiotensin-converting enzyme inhibitor (ACEI) is a logical choice.
- *Whether there are specific contraindications or cautions*: in a patient with hypertension and diabetes, a thiazide diuretic or a non-selective beta-blocker would be less suitable, since they can affect blood sugar control.
- *Whether there are possible drug interactions*.
- *Whether the drug offers a good benefit-to-harm balance*.

How is the benefit-to-harm balance estimated?

Five factors determine the benefit-to-harm balance:

- the seriousness of the problem to be treated
- the efficacy of the drug
- the seriousness and frequency of possible adverse effects
- the safety of other drugs that might be used instead, and
- the efficacy of other drugs that might be used instead.

The balance is favourable if the disease is life-threatening, the drug highly effective and the only one available, and the risk of serious adverse effects negligible. The balance is unfavourable if the disease is trivial, the drug poorly effective and there are more effective and safer competitors, and the risk of serious adverse effects high. Most cases lie somewhere between these two extremes. In using published data to estimate the benefit-to-harm balance, remember that:

- patients in clinical trials are selected and may not be representative of your patient
- clinical trials focus on therapeutic effects and are less good at eliciting adverse effects
- factors in the individual patient can alter the benefit-to-harm balance (see below).

Nevertheless, the best available information has to be used in making a decision. An example is the treatment of breast cancer with tamoxifen. The disease is serious, tamoxifen is efficacious (number needed to treat to prevent one death 17), and it has some serious but uncommon adverse effects (number needed to harm (NNH) to cause one case of endometrial cancer 143, NNH to cause one venous thrombosis 130). The benefit-to-harm balance is favourable, but the safety and efficacy of other drugs must also be considered. For example, if the risk of thromboembolism is high in an individual woman, anastrozole may be a better choice than tamoxifen.

What are the principles that dictate the dosage regimen?

It is generally best to start with a dosage at the lower end of the recommended range and increase the dosage slowly, monitoring the therapeutic effect at regular intervals and looking for adverse effects. If adverse effects occur, the dosage should be reduced or another drug tried. It is sometimes possible to use lower dosages by combining drugs (eg azathioprine reduces glucocorticoid dosage requirements in immunosuppression).

Think of drug interactions and avoid potentially dangerous combinations.

Key Points

Dosage regimens should generally be individualised, depending on features of the patient that can alter the drug's pharmacokinetics (disposition in the body) or pharmacodynamics (therapeutic and adverse effects)

It is usually good practice to start with a low dose, gradually increasing it according to response; a loading dose can produce a response more quickly if necessary

The most important factors that alter drug pharmacokinetics are renal insufficiency and liver disease

The most important factors that alter drug pharmacodynamics are fluid and electrolyte abnormalities, age and liver disease

Careful monitoring can help to avoid adverse drug reactions and interactions during long-term therapy, particularly if the disease changes with time

The more even the balance of benefit to harm, the more care needs to be taken in monitoring therapy

KEY WORDS: benefit-to-harm balance, dosage regimens, monitoring drug therapy

Remember that pharmacokinetic and pharmacodynamic variability can alter dosage requirements (see below). Take particular care with drugs that have a low therapeutic index. Monitor progress during long-term therapy and be prepared to alter doses if necessary or to withdraw therapy.

When is a loading dose appropriate?

Some drugs are given as a loading dose, followed by a maintenance dosage. Use a loading dose when the time to steady state (about four half-lives) is longer than you are prepared to wait. Examples include:

- digoxin (half-life 40 hours with normal renal function)
- amiodarone (half-life weeks)
- warfarin (half-life 24 hours).

With warfarin, a loading dose also allows more careful monitoring of therapy during the early phases of therapy when the eventual therapeutic dose is neither known nor predictable.

In each of the above cases the loading dose is given not as a single dose but in divided doses at intervals. The loading dose should be reduced when the apparent volume of distribution is reduced (eg digoxin in severe renal insufficiency).

A loading dose is also used when a large initial pharmacodynamic effect is desirable. For example, use large initial doses of carbimazole and glucocorticoids, then reduce to a maintenance dosage.

How do pharmacokinetic changes alter dosage regimens?

Pharmacokinetic changes are alterations in the disposition of a drug in the body. They can occur through ageing, organ pathology or drug interactions. Changes that commonly affect dosage regimens involve reduced drug clearance through impaired renal or hepatic function or drug interactions. Children often have different pharmacokinetics to adults. Examples include:

- In *gastrointestinal disease* changes in the extent of drug absorption will alter the amount of drug in the body. Such changes are highly variable: for example, in coeliac disease cefalexin and propranolol are more extensively absorbed, digoxin and thyroxine less extensively.
- A *change in clearance* alters the amount of drug in the body and the steady-state plasma concentration; if clearance is reduced (eg through renal insufficiency), the maintenance dose should be decreased (Fig 1). In patients with renal insufficiency, long-term treatment with drugs that are eliminated unchanged by the kidneys (eg digoxin, lithium, metformin) should be avoided if possible. If the clearance of a drug is reduced, the half-life will be prolonged and it will take longer to reach steady state.
- *Severe liver disease* alters the pharmacokinetics of some drugs by reduced metabolism (eg opioids, statins) and reduced protein binding (which increases the amount of drug available for clearance). Drugs affected by both processes should be avoided (eg warfarin and phenytoin). Reduced protein binding of phenytoin also alters the interpretation of the serum concentration, which measures total phenytoin and not the active (unbound) concentration. Most other commonly used drugs are unaffected by hypoalbuminaemia. Intrahepatic shunting reduces the first-pass inactivation of drugs that are highly cleared by the liver (eg clomethiazole, morphine). Conversely, prodrugs (eg ACEIs) will not be activated if there is impaired metabolism, making therapy difficult.
- In *thyrotoxicosis* the metabolism of some drugs (eg beta-blockers) is increased and higher doses are needed.
- In rare cases the *volume of distribution* of a drug is altered by disease or drug interactions; this also alters the half-life (a lower volume shortens the half-life). A good example is digoxin in severe renal insufficiency, slightly mitigating the

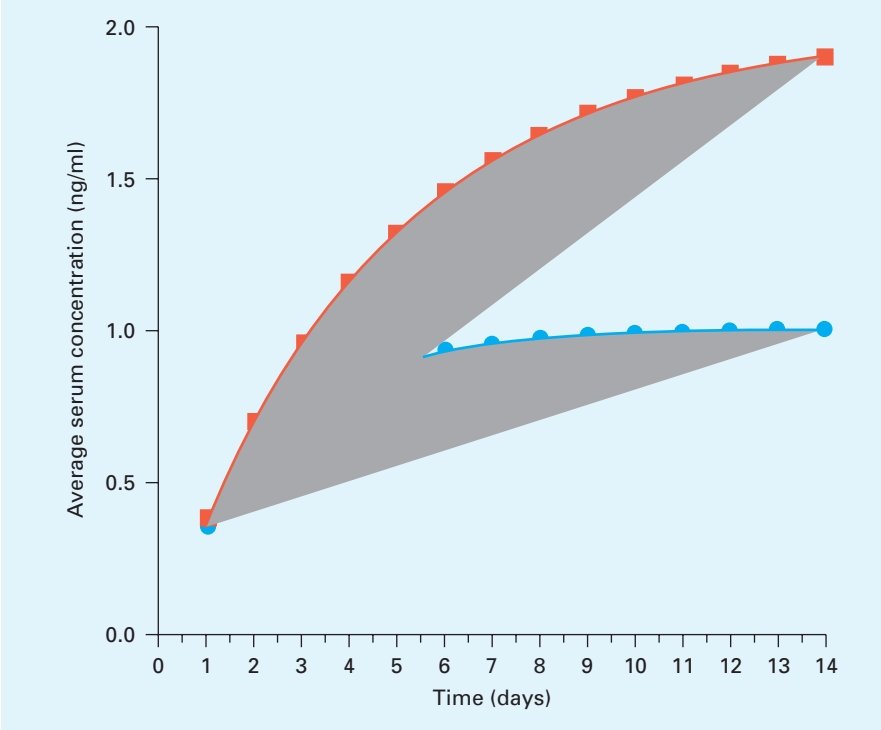

Fig 1. Predicted average serum digoxin concentrations during daily administration of 0.25 mg to a patient with normal renal function (circles) and one with 50% renal impairment (squares).

prolongation of half-life from reduced clearance. This stresses the need for careful monitoring or avoidance of the drug in such cases.

How do pharmacodynamic changes affect dosage regimens?

Pharmacodynamic changes are alterations in tissue response to a drug by a shift in the dose-response curve. They can occur through ageing, altered physiology, organ pathology or drug interactions. Children sometimes have different pharmacodynamic responses to adults. Examples include:

- *Altered fluid and electrolyte balance*: for example, potassium depletion shifts the dose-response curve for digoxin to the left, making the heart more sensitive to its effects (Fig 2).
- *Altered physiological responses*: for example, changes in blood pressure control with age can lead to postural hypotension, especially if accompanied by fluid depletion.
- *Liver disease*: for example, reduced clotting factor production increases sensitivity to warfarin.
- *Changes in target organ responsiveness*: for example, nitrate tachyphylaxis – this can be avoided by giving nitrates in the morning and early evening, allowing a drug-free period overnight.
- *Progression or remission of disease*: for example, progressive Lewy body dementia increases the risk of dyskinetic effects of neuroleptic drugs.

Adverse effects can be avoided in such cases by starting with a dose at the lower end of the recommended range, and monitoring carefully for responses while slowly increasing the dose to maximise benefit.

Principles that underlie the monitoring of drug therapy

The more even the balance of benefit to harm, the more care needs to be taken in monitoring therapy (Fig 3).

In monitoring therapy, choose clear end-points relevant to the well-being of the patient in assessing therapeutic or adverse effects. In general, clinical end-points are preferable to laboratory surrogates, for example measuring the frequency of seizures or attacks of asthma rather than the serum carbamazepine or theophylline concentration.

If there is no simple clinical end-point, try to find a measure of the tissue pharmacodynamic effect of the drug: for example, the international normalised ratio is a measure of the pharmacological effect of warfarin and relates to toxic effects but is not a good predictor of therapeutic effect. If there is no pharmacodynamic end-point, it may be possible to measure the plasma concentration of the drug (a pharmacokinetic end-point). This is useful for a few drugs, including aminoglycosides, ciclosporin, digoxin, lithium and phenytoin. It is good for assessing adherence to therapy and, in some cases, toxicity.

Remember that the effects of treatment can change with time:

- a disease can progress or remit

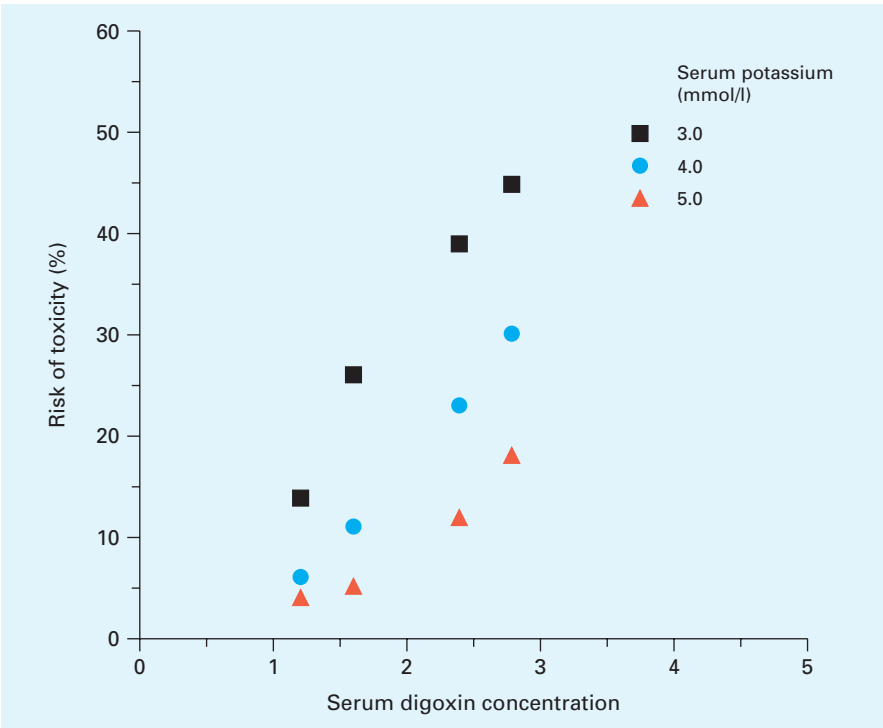

Fig 2. The effect of serum potassium concentration on the risk of toxicity at different serum digoxin concentrations.

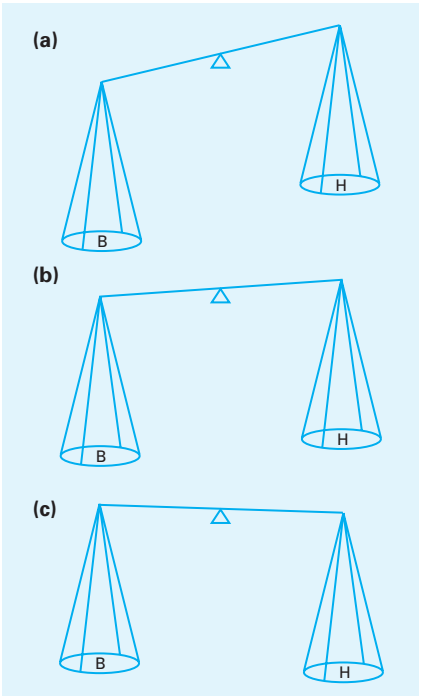

Fig 3. The benefit (B) to harm (H) balance in drug therapy: (a) highly favourable, no monitoring or only occasional monitoring required; **(b)** highly favourable, careful monitoring required; **(c)** unfavourable, drug contraindicated.

- adverse effects can be associated with long-term treatment
- drug interactions can alter drug effects, both pharmacokinetic and pharmacodynamic.

Regular monitoring is necessary to ensure that the effects of treatment remain stable; drug dosages should be altered when they do not. Remember that the balance of benefit-to-harm can change with time.

Conflicts of interest

None.

Further reading

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Adverse drug interactions

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Background

The average prescription for elderly patients who are taking five or more medicines is likely to have some potential for drug interactions. It is not always clear from the computerised programmes widely adopted by pharmacists, which do not grade interactions according to their clinical importance, whether this is of sufficient import to justify an alteration in drug choice, a modification of dosage or initiation of special surveillance. On the other hand, when harm arises, judicial review in this area continues to ascribe the major responsibility to the prescriber rather than to the dispenser. The British National Formulary Appendix 1[1] highlights reactions that may be of clinical relevance, but even this source lists interactions that may not be of sufficient importance to modify drug choice.

Clinical relevance

In a recently published prospective study of 18,820 patients admitted to hospital, the prevalence of adverse drug reactions was 6.5%, with the reaction leading directly to admission in some 80% of cases.[2] Low-dose aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and warfarin headed the list of culprits. Of these adverse reactions, one in six was due to a drug–drug interaction. Common examples are shown in Table 1.

Interference of one drug by another can lead to a spectrum of responses, from an enhanced effect which may be toxic but is sometimes beneficial, to a reduced effect that results in lack of efficacy. In some cases, the onset may be subtle, for example, reduced plasma levels of ciclosporin or protease inhibitors. The ultimate consequences, rejection of a transplanted organ or reactivation of HIV infection, are not immediate. There are no early warning signs and only in certain settings will the 'all or none' consequences occur. The persistent induction of liver drug metabolising enzymes by, say, anti-epileptics, may come to light only in a non-therapeutic setting such as paracetamol overdose with an increased likelihood of hepatotoxicity. The potential for interaction extends beyond prescription medicines

Key Points

- **Drug interactions should be anticipated**
- **The British National Formulary and pharmacy computer programmes should be used for reference**
- **Clinical problems arise with (i) risky drugs (warfarin, non-steroidal anti-inflammatory drugs, digoxin) and (ii) risky patients (elderly, those with renal insufficiency)**
- **The mechanisms most commonly involved are hepatic: cytochrome P450 induction/inhibition**
- **The P-glycoprotein transporter system is now implicated**
- **The final decision rests with the prescriber**

KEY WORDS: cytochrome P450, drug interaction, P-glycoprotein