MEASURING PLASMA DRUG CONCENTRATIONS

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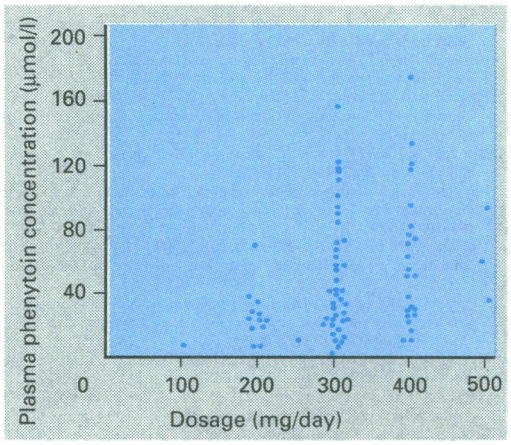


Plasma phenytoin concentrations at steady state in relation to total daily dose. At all dosages there are large variations in mean steady state concentration from subject to subject.

Factors that modify drug plasma concentration for a given dose

- Drug formulation
- Drug interactions
- Environmental factors
- Genetic variation
- Renal and hepatic function

If a given dose of a drug produced the same plasma concentration in all patients there would be no need to measure the plasma concentration of the drug. However, people vary considerably in the extent to which they absorb, distribute, and eliminate drugs. Tenfold or even greater differences in steady state plasma concentrations have been found among patients treated with the same dose of important drugs such as phenytoin, warfarin, and digoxin. The following are some of the many reasons for these differences.

Formulation—Some drugs—for example, digoxin—are better absorbed from liquid formulations than from tablets. Phenytoin toxicity has been reported after a chemical change in a supposedly inert excipient (calcium sulphate to calcium lactose) in phenytoin capsules.

Genetic variation—For example, in some people drugs are acetylated slowly, in others they are acetylated quickly. Drugs whose metabolism is affected by acetylation include hydralazine, procainamide, and isoniazid.

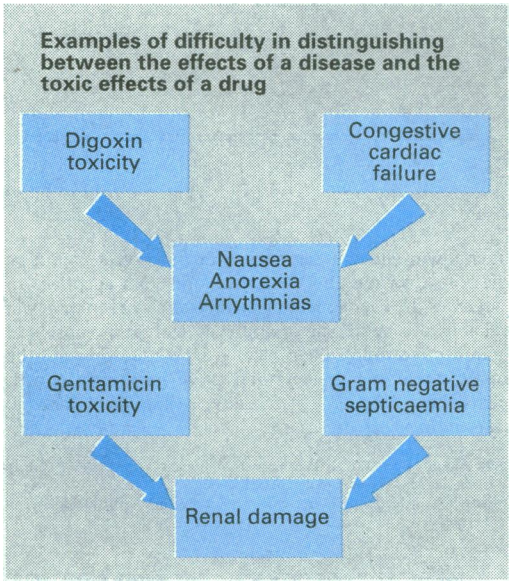
Environmental variation—For example, smoking increases the rate of clearance of theophylline.

Effects of disease—The pharmacokinetics of some drugs may be altered by disease—for example, renal impairment decreases the rate of elimination of gentamicin, digoxin, and lithium. In patients with hepatic disease the metabolism of drugs such as phenytoin and carbamazepine may be reduced, resulting in increased plasma concentrations.

Drug interactions—For example, quinidine and verapamil increase the plasma concentration of digoxin by interfering with its renal elimination; diuretics increase the plasma concentration of lithium by interfering with its renal excretion.

Measuring the plasma concentration of a drug allows the doctor to tailor the dosage to the individual patient and to obtain the maximum therapeutic effect with minimal risk of toxicity.

Clinical usefulness



There is only a small number of drugs for which measuring the plasma concentration is helpful in clinical practice. The following criteria must be satisfied for the plasma concentration of a drug to be useful.

(1) *Difficulty in interpreting clinical evidence of therapeutic or toxic effects*—If it is easy to measure the therapeutic or toxic effects of a drug directly the plasma drug concentration gives little additional information about drug action—for example, there is little point in measuring the plasma insulin concentration in a diabetic patient as blood glucose measurements give a direct indication of the short term action of the drug. On the other hand, it is difficult to measure the therapeutic effects of phenytoin, and measuring the plasma concentration helps to tailor the dose within the appropriate therapeutic range.

Occasionally it may be difficult to distinguish between the effects of a disease and the toxic effects of a drug—for example, renal failure may occur in a patient with a Gram negative septicaemia, either because of the disease or because of an adverse effect of the gentamicin used to treat it; both congestive cardiac failure and digoxin toxicity may produce nausea, anorexia, and arrhythmias. In these cases the plasma drug concentration will provide important information that is not obtainable by any other means and will allow appropriate alterations in drug dosages to be made.

Measuring plasma drug concentrations

Measurement of proved value

Aminoglycoside antibiotics:
- Gentamicin
- Kanamycin

Anticonvulsants:
- Phenytoin
- Carbamazepine

Digoxin and digitoxin

Lithium

Theophylline

Cyclosporin

Thyroid hormones

Sometimes measured but case not proved

Antiarrhythmic drugs:
- Lignocaine
- Procainamide
- Quinidine
- Amiodarone

Anticonvulsants other than phenytoin and carbamazepine

Methotrexate

Tricyclic antidepressants

Flucytosine

(2) *A good relation between the plasma concentration of a drug and either its therapeutic or its toxic effect*—There is little point in measuring the plasma drug concentration if it will not give interpretable information about the therapeutic or toxic state of the patient—for example, if there is a subtherapeutic concentration of digoxin in a patient with compensated heart failure with sinus rhythm digoxin may be withdrawn without fear that the patient's heart failure will worsen; a high peak concentration of gentamicin is associated with toxic effects and prompts early adjustments to dosage.

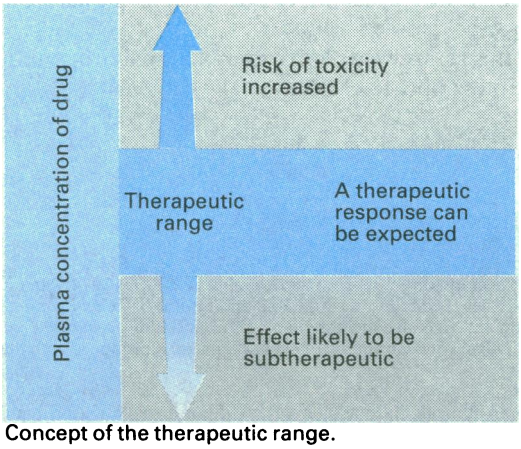
(3) *A low toxic to therapeutic ratio*—Though there are several drugs for which the first two criteria apply, measurement of plasma concentration may not be useful for them all—for example, while in some cases there may be a good relation between plasma concentration of penicillin and its therapeutic effect, the dosage range over which penicillin is safe is so large that very high dosages can be given safely. On the other hand, for some drugs (such as lithium, gentamicin, phenytoin, and digoxin) there is only a small difference between the concentrations that are associated with therapeutic effects and those associated with toxic effects.

(4) *The drug should not be metabolised to active metabolites.*—Even if a drug satisfies the three criteria above interpretation of the plasma drug concentration may be rendered difficult by the presence of metabolites with therapeutic or toxic activity. If active metabolites are produced both the parent drug and the metabolites would have to be measured to provide a comprehensive picture of the relation between the total plasma concentration of active compounds and the clinical effect. This is usually not possible in routine monitoring and limits the usefulness of plasma concentration measurements of, for example, procainamide, which is metabolised to N-acetylprocainamide (acecainide), which has equipotent antiarrhythmic activity.

Therapeutic range

Factors that modify the effect of the drug for a given drug plasma concentration

- Drug interactions
- Electrolyte balance
- Acid-base balance
- Age
- Bacterial resistance
- Protein binding (if total concentration measured)



Concept of the therapeutic range.

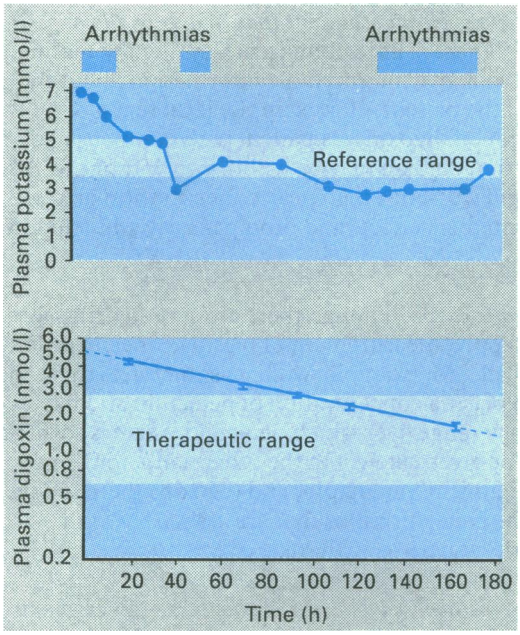
Laboratories quote reference ranges for biochemical measurements. The reference range is the range of values which encompasses 95% of the values found in a large number of healthy people.

There is an analogous method of expression for plasma drug concentration—the therapeutic range. This is derived from measurements in large numbers of patients in carefully controlled studies and is the range within which a therapeutic effect is expected to occur with a minimal risk of toxicity. For example, longitudinal studies in patients with generalised seizures have shown improved seizure control when the plasma phenytoin concentration is increased above 40 μmol/l, and as clinical signs of toxicity increase in frequency at concentrations above 80 μmol/l, 40-80 μmol/l is the therapeutic range.

By analogy with the concept of a reference range the therapeutic range is often assumed to apply to all patients in all circumstances. However, this may not always be so. For example, plasma phenytoin concentrations below 40 μmol/l are sufficient to achieve complete control of seizures in some patients with relatively mild epilepsy while some patients may require concentrations above 80 μmol/l.

A further consideration is that there are often features which are specific to an individual patient and which may alter his or her therapeutic range. The therapeutic range is derived from studies of populations and provides only a guide to those concentrations that may be expected to be associated with a therapeutic effect and to the concentrations above which toxic effects may occur. The tailoring of drug dosages to an individual must take into account those features that are unique to that person, including relevant biochemical measurements and clinical factors.

Obviously a patient who is taking phenytoin and who exhibits classic signs of toxicity, such as nystagmus and ataxia, requires a reduction in the dose regardless of whether the plasma concentration is within the therapeutic range.



Plasma potassium and digoxin concentrations in a patient after a single intravenous dose of digoxin 0·5 mg. Arrhythmias occurred when the digoxin concentration was high or the potassium concentration low.

Factors that modify the therapeutic range

If the effect of a drug at its site of action is altered for a given concentration the therapeutic range will change. Factors that may alter this concentration-response relation include:

Electrolyte balance—For example, the effects of many antiarrhythmic drugs (such as lignocaine, quinidine, and procainamide) are altered in the presence of hypokalaemia, as are the effects of digoxin.

Acid-base balance—For example, acidosis enhances the effect of digoxin.

Age—For example, there is increased sensitivity to digitalis in elderly people.

Bacterial resistance—For example, although the plasma concentration of gentamicin may be adequate, an organism that is resistant to gentamicin will not be affected.

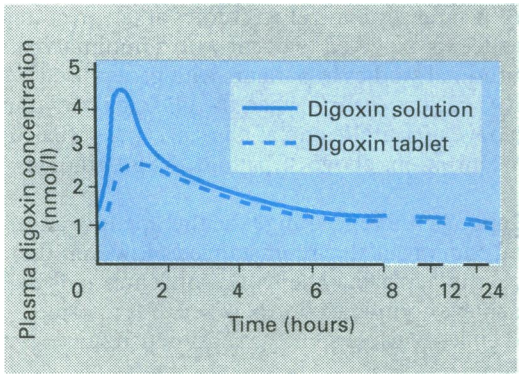
Plasma protein binding—It is usual when measuring plasma drug concentrations to measure the total amount of drug in the plasma (that is, protein bound and unbound drug). However, the therapeutic effect is largely determined by the unbound concentration. If protein binding changes the ratio of bound to unbound drug will change, and this will alter the interpretation of the plasma concentration of total drug (this is discussed more fully in the article on phenytoin).

Timing of measurements

Calculation of the length of time it takes to reach steady state

Example

Digoxin has a half life of about 40 hours in a patient with normal renal function. If treatment is given by a daily maintenance dose without an initial loading dose it will take 5×40 hours, or about eight days to achieve steady state



Plasma digoxin concentrations during the 24 h after a single dose during daily maintenance dose therapy. In the 6 h after administration the concentration is a poor guide to the mean steady state concentration.

How long after starting treatment should plasma concentration be measured?

If you give a drug repeatedly it will accumulate in the body. Eventually, when the amount being given is equal to the amount being eliminated an equilibrium or "steady state" is reached. The time required to reach this steady state depends only on the half life of the drug. After five half lives over 95% of a drug will have accumulated, and for practical purposes steady state can be considered to have been achieved.

The plasma concentration can be measured before this steady state has been reached, but the timing of the sample will have to be taken into consideration when interpreting the result.

How long after the last dose should the sample be taken?

It is preferable to have a sample that reflects the mean steady state concentration during a dosage interval. If the sample is taken too soon after the last dose (for example, at the time of the peak or maximum steady state concentration) it will not have the mean concentration. It is usually simplest to take a sample just before the next dose is due, as this is a reliable measure of the minimum steady state concentration (a "trough" concentration), even though it slightly underestimates the mean steady state concentration. For aminoglycoside antibiotics both peak and trough concentrations are important.

In subsequent articles in this series we will discuss individual drugs and show how these basic principles apply to each.

The sources of the data shown in the graphs are W D Hooper *et al, Aust N Z J Med* 1974;**4**:449 for plasma phenytoin concentrations *v* dosage; J K Aronson, D G Grahame-Smith, *Br J Clin Pharmacol* 1976;**3**:1045-57 for plasma potassium and digoxin concentrations *v* time; and Lloyd *et al, Am J Cardiol* 1978;**42**:129-36 for plasma digoxin concentration *v* time. The data are reproduced with the permission of the journals.

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