# MAKING THE MOST OF PLASMA DRUG CONCENTRATION MEASUREMENTS

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**Criteria that a drug should satisfy for plasma concentration measurements to be useful**

- Difficulty in interpreting clinical evidence of therapeutic or toxic effects
- A good relation between the plasma drug concentration and the therapeutic or toxic effect, or both
- A low toxic:therapeutic ratio
- Does not metabolise to important active metabolites

In the previous articles in this series we have outlined the principles of monitoring drug therapy by measuring the plasma drug concentration and shown how they can be applied to specific drugs (digoxin, lithium, theophylline, phenytoin, aminoglycoside antibiotics, and cyclosporin), for which the criteria in the box are sufficiently fulfilled to justify monitoring.

## Usefulness of measurement

**Indications for measuring plasma drug concentrations**

- Monitoring compliance
- Individualising therapy
  —during early therapy
  —during dosage changes
- Diagnosing undertreatment
- Avoiding toxicity
- Diagnosing toxicity
- Monitoring and detecting drug interactions
- Guiding withdrawal of therapy

When the criteria are not rigorously met the regular use of plasma drug concentration measurements is hard to justify. None the less, measurements are sometimes made for other drugs, including anticonvulsants such as carbamazepine and ethosuximide; antiarrhythmic drugs; tricyclic antidepressants; and methotrexate. These are drugs which fulfil some but not all of the criteria. In some circumstances, however, their measurement may be helpful (for example, in monitoring compliance).

Even for drugs that fulfil the criteria there is some controversy about the usefulness of monitoring their plasma concentrations.

Firstly, it has been argued that there is no good evidence that targeting plasma concentrations improves the therapeutic outcome[1,2] and that the hypothesis that it is of therapeutic value needs to be tested.[3] These arguments ignore the axiom, which implies that there is a better relation between concentration and effect than between dose and effect, implying that it should be possible to improve therapy with a drug by monitoring its plasma concentrations. In practice, however, the benefit to be gained is likely to be small when the drug does not fulfil the necessary criteria. There is certainly a need for prospective studies to determine the benefit of monitoring drug concentrations, though there would be considerable practical and ethical difficulties in designing such studies.

Treat the patient, not the plasma drug concentration

Secondly, it is argued that the value of the technique is reduced by problems in defining therapeutic ranges—for example, when there are conditions that alter a drug's pharmacodynamic effects.[2,3] But this argument merely emphasises the need for proper interpretation of plasma drug concentrations in these conditions.

Thirdly, it has been said that too often it is the plasma concentration which is treated rather than the patient[4] and that much monitoring is rendered useless by, for example, inappropriate timing of sampling.[3] That this is so is evidence that plasma drug concentration monitoring is being misused rather than that it is of no use.

Routine measurement of the plasma drug concentration without a clear purpose is as bad as no measurement at all

There is no justification for routine measurements of plasma drug concentrations without a definite purpose. For example, in an epileptic patient taking phenytoin who is free of fits and is otherwise well routine measurement is of little value and indeed may lead to inappropriate adjustments of dosage. However, it may be of value when, for example, an interacting drug is introduced or when a dosage adjustment is required in a patient whose fits are poorly controlled.

The indirect benefits of measuring the plasma drug concentration include education of the doctor in the principles underlying dose responsiveness and the detection of important new drug interactions.[1] The use of such measurements in research is outside the scope of these articles.

## How to use the measurements properly

### Timing of blood samples

*Aminoglycoside antibiotics*
Intravenous: Peak—15 min after the end of the infusion; trough—just before the next dose
Intramuscular: Peak—1 h after the injection; trough—just before the next dose

*Cyclosporin*—Just before the next dose; measure at the same time of day on each occasion (for example, before the morning dose)

*Digoxin*—At least 6 h after the last dose (it is therefore best to give a single daily dose in the evening)

*Lithium*—Exactly 12 h after the last dose

*Phenytoin*—Timing is not important

*Theophylline*
During an infusion: 4-6 h after starting the infusion; stop infusion for 15 min before taking the sample
Oral: just before the next dose; measure at the same time of day on each occasion

If plasma drug concentration measurements are to be of any value attention must be paid to the timing of blood sampling, the type of blood sample, the measurement technique, and interpretation of the result.

*Timing of sampling*

It is important to take the blood sample for drug measurement at the correct time after dosing. This has been dealt with for each drug in previous articles, and the appropriate timings are summarised in the box. Errors in timing are probably responsible for the greatest number of errors in interpreting results.

*Types of samples*

For most drugs the blood sample can be taken into a heparinised tube or allowed to clot, and there are no important restrictions on storage before measurement. For lithium and aminoglycosides, however, samples should be allowed to clot and separated within an hour. For cyclosporin it is important to consult the local laboratory for details on sampling technique.

### Types of samples required

| *Drug* | *Type of sample* |
|---|---|
| Digoxin, phenytoin, theophylline | Plasma or serum |
| Aminoglycoside antibiotics, lithium | Serum |
| Cyclosporin | Whole blood or plasma (consult your laboratory) |

*Measurement technique*

For the laboratory's part it is important to ensure that the assay used is as reliable and specific as possible and that appropriate quality control is undertaken. Assay results should be available quickly and preferably within 24 hours of receiving the sample, as the most important uses of measurement are during dosage adjustments and in diagnosing toxicity, when rapid decisions need to be made. Indeed, there is evidence that on site measurement of antiepileptic drugs has an immediate impact on clinical decision making.[5]

### Examples of interpreting low plasma drug concentrations

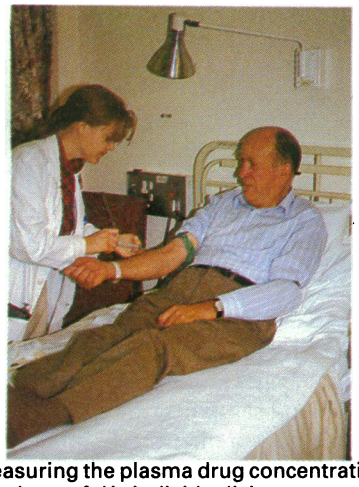
1 *Patient with atrial fibrillation taking digoxin*
Ventricular rate=75 beats/min
Plasma digoxin concentration=0·6 nmol/l
*Discussion*—It would be better to withdraw the drug than to increase the dosage to achieve a "therapeutic" plasma concentration as it is unlikely that digoxin at such low plasma concentration is contributing to slowing the heart rate. Withdrawal is unlikely to result in deterioration

2 *Patient taking phenytoin*
Patient with epilepsy, free of fits for 12 months. Plasma phenytoin concentration= 25 μmol/l
*Discussion*—There may be therapeutic benefit in patients with plasma concentrations below the therapeutic range and withdrawal may lead to recurrence of fits. Treatment should probably be continued.

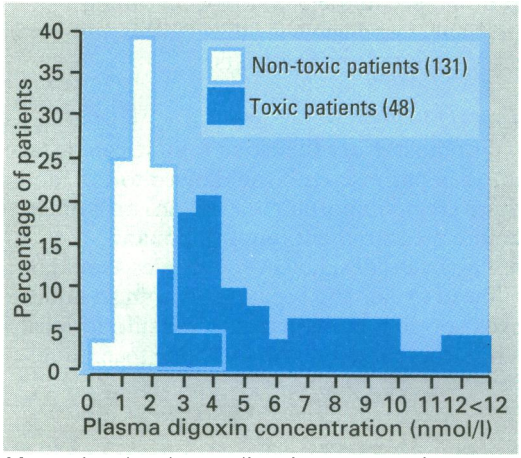
*Interpretation of the result*

The most important principle in interpreting the plasma drug concentration is that the treatment should be tailored to the patient's needs. In doing so you should take into account not only the concentration but also other clinical features that may affect the relation between concentration and effect. It would be wrong to use the concentration measurement in isolation and to try to engineer the plasma concentration into a predetermined range (see example in the box). It is important therefore for the doctor responsible to know how to interpret the result in the light of the patient's condition.

## Indications for measurement



Measuring the plasma drug concentration may be useful in individualising treatment.




Measuring the plasma digoxin concentration may be helpful in confirming the diagnosis of toxicity.

**Examples of factors that affect target ranges for plasma drug concentrations**

| *Drug* | *Factor* |
|---|---|
| Aminoglycoside antibiotics | Other nephrotoxic drugs (enhance the risk of renal damage) |
| Cyclosporin | Other nephrotoxic drugs (enhance the risk of renal damage) |
| Digoxin | Potassium depletion |
| Lithium | Electroconvulsive therapy (may enhance the action of lithium) |
| Phenytoin | Altered protein binding (for example, in chronic renal failure) |

There are several circumstances in which plasma drug concentration measurement may be helpful, although each indication does not apply equally to each drug.

*Compliance*—In the article on compliance we discussed the ways in which compliance may be monitored. Measuring the plasma concentration may be helpful as a low measurement reflects either poor recent compliance or undertreatment. Poor compliance is implicated if the patient is taking a dose which is unlikely to be associated with such a low concentration or if previous measurements suggest that the plasma concentration should be higher for the given dose.

*Individualising therapy*—When starting drug therapy it may be useful to measure the plasma concentration in order to tailor the dosage to the individual. This applies to all drugs, although it is most important for lithium, cyclosporin, and the aminoglycoside antibiotics. If for any reason at a later stage the dosage regimen has to be altered (for example, in patients with renal failure) plasma concentration measurement may again be helpful.

*Diagnosing undertreatment*—Undertreatment of an established condition may often be diagnosed on observing a poor clinical response. However, when the drug is being used as prophylaxis you cannot observe the response and may have to settle for giving a dosage that will produce a target plasma concentration. This applies particularly to lithium in preventing manic depressive attacks, to phenytoin in preventing fits after neurosurgery or trauma, and to cyclosporin in preventing transplant rejection.

*Avoiding toxicity*—In all cases measurement during the early stages of treatment allows you to avoid plasma concentrations likely to be associated with toxicity.

*Diagnosing toxicity*—In many cases drug toxicity can be diagnosed clinically. For example, it is usually easy to recognise acute phenytoin toxicity, and measuring the plasma concentration may not be necessary for the diagnosis, although it may be helpful in adjusting the dosage subsequently. On the other hand, digoxin toxicity may mimic some of the effects of heart disease, and measuring the plasma concentration in cases in which toxicity is suspected may be helpful in confirming the diagnosis. Similarly, nephrotoxicity due to aminoglycoside antibiotics is hard to distinguish clinically from that caused by a severe generalised infection, and the plasma concentration may help to distinguish the two.

*Drug interactions*—If a potentially interacting drug is added measurement of the plasma concentration may guide subsequent changes in dosage. For example, when giving a thiazide diuretic to a patient taking lithium, measurement of the plasma lithium concentration will help to avoid toxicity. This also applies to theophylline when erythromycin is added. Conversely, measurement of the whole blood cyclosporin concentration will help to avoid undertreatment if rifampicin is added.

*Stopping treatment*—Measurement of the plasma drug concentration may guide when to stop treatment in two circumstances.

(1) When the plasma concentration is below the therapeutic range in a well patient. For example, if the plasma digoxin concentration is below the therapeutic range in a patient whose clinical condition is satisfactory then withdrawal of digoxin is unlikely to lead to clinical deterioration. Note that this use of the plasma concentration measurement depends on the concept that there is a lower end to the therapeutic range. This is not always the case—while it is probably true for digoxin it is not true for other drugs, particularly phenytoin (see box on previous page).

(2) When the plasma concentration is high without therapeutic benefit. For example, if there is no response to lithium and the serum concentration is at the upper end of the therapeutic range increased dosage is unlikely to be beneficial and the risk of toxicity is high. Withdrawal of lithium and the use of different treatment would be justified.

## Conclusions

**Therapeutic and toxic plasma concentrations of commonly measured drugs**

| Drug | Concentration below which a therapeutic effect is unlikely | Concentration above which a toxic effect is more likely |
|---|---|---|
| Aminoglycosides: | | |
| Amikacin | 34 μmol/l (20 μg/ml) (at peak)<br>17 μmol/l (10 μg/ml) (at trough) | 55 μmol/l (32 μg/ml) (at peak) |
| Gentamicin | 5 μg/ml (at peak)<br>2 μg/ml (at trough) | 12 μg/ml (at peak) |
| Kanamycin | 50 μmol/l (25 μg/ml) (at peak)<br>20 μmol/l (10 μg/ml) (at trough) | 80 μmol/l (40 μg/ml) (at peak) |
| Cardiac glycosides: | | |
| Digitoxin | 20 nmol/l (15 ng/ml) | 39 nmol/l (30 ng/ml) |
| Digoxin | 1·0 nmol/l (0·8 ng/ml) | 3·8 nmol/l (3 ng/ml) |
| Cyclosporin* | 80-200 nmol/l (100-250 ng/ml) | 170-330 nmol/l (200-400 ng/ml) |
| Lithium | 0·4 mmol/l | 1·0 mmol/l |
| Phenytoin | 40 μmol/l (10 μg/ml) | 80 μmol/l (20 μg/ml) |
| Theophylline | 55 μmol/l (10 μg/ml) | 110 μmol/l (20 μg/ml) |

*Measured in whole blood by specific radioimmunoassay or high performance liquid chromatography. The actual results depend on the laboratory in which the measurement is made.

In this series we have outlined the uses of measuring the plasma concentrations of some drugs and given guidelines on how such measurements should be made and interpreted.

The box summarises the target plasma concentrations for each of the drugs. In each case there is a concentration below which a therapeutic effect is unlikely and a concentration above which the risk of toxicity is high. These two concentrations imply a therapeutic range for each drug, but remember that there are circumstances in which strict adherence to a range of this kind is inappropriate. The plasma concentration should always be interpreted in the light of factors which may alter the effective therapeutic range.

Nor is it always necessary to measure plasma concentrations to achieve satisfactory drug therapy. Routine measurement without a clear purpose is as bad as no measurement at all. The application of the principles we have outlined should allow the rational use of plasma concentration measurement in optimising drug therapy.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# *Medical Education*

## Assessment of students


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*This is the fifth in a series of articles examining the problems in medical education and their possible solutions*


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Student assessment is often described as "the tail that wags the dog" of medical education. It is seen as the single strongest determinant of what students actually learn (as opposed to what they are taught) and is considered to be uniquely powerful as a tool for manipulating the whole education process. Sir William Osler summed up the power of examinations in 1913: "At the best means to an end, at the worst the end itself, they may be the best part of an education or the worst—they may be its very essence or its ruin."[1] But is assessment as powerful as we think, and, if it is, are most medical educators using it effectively?

### Why assess?

Few people formally question why we assess medical students, and many who do think no further than using assessment as a means of checking that required information has been learnt. Certainly in an overloaded curriculum students will pay attention to topics that they know will feature in examinations.[2] A recent study of surgical students at the Flinders University of South Australia found that when no clear guidelines and course objectives were given in a self directed learning programme the students—far from exploring the topic widely and pursuing personal interests—tried to "guess" what would feature in the final examination and concentrated on that (D J Prideaux, paper presented at fifth Ottawa international conference on assessment of clinical competence, Dundee, September 1992). This tendency allows staff to direct students' attention to important topics but also increases the risk that unexamined areas will be ignored.

Unfortunately, the fact that students can successfully answer examination questions on a topic is no guarantee that they will retain their knowledge of the subject. Assessments that are based on a one off factual recall are notoriously unreliable as indicators of real learning,[3] and if assessment is to be used to ensure learning more complex approaches are needed. One method is to retest the same information at regular