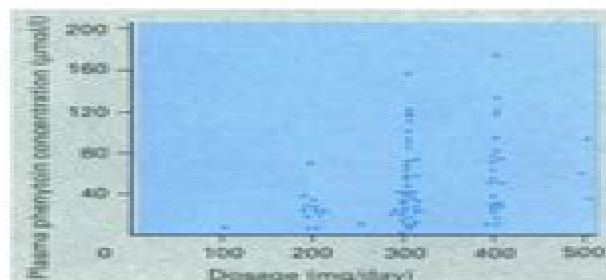


MEASURING PLASMA DRUG CONCENTRATIONS

J K Aronson, M Hardman



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.

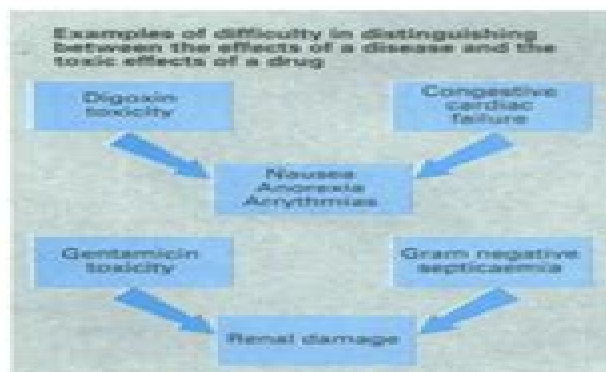
Environmental variation—For example, smoking increases the rate of clearance of theophylline.

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.

Abc Of Monitoring Drug Therapy

**Paul P. Glasziou, Les Irwig, Jeffrey K.
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