

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) refers to the measurement of drug concentrations in biological fluids with the goal of optimising a patient's drug therapy and clinical outcomes. Drugs where TDM is used include those with a narrow therapeutic index, concentration-dependent pharmacokinetics, or where the desired therapeutic effect is difficult to monitor or there are large pharmacokinetic variations between individuals.

For measurement of drug concentrations to be useful clinically, there should be a relationship between dose, plasma or blood concentration and pharmacological effects. Variations in response between individuals at any given concentration means that a range of concentrations (the therapeutic range) is targeted. This range represents drug concentrations which are effective for a particular indication in the majority of patients, without a significant risk of toxicity. During January 2010 there was a change from mass to molar units for some TDM reports from SA Pathology due to the use of different analysers. Therapeutic ranges for some commonly measured drugs which have been affected by this change are summarised below.

Drug	“Old” therapeutic range (mass units)	“New” therapeutic range (molar units)
Valproate	50-100 mg/L	300-600 micromoles/L
Phenytoin	10-20 mg/L	40-80 micromoles/L
Carbamazepine	5-12 mg/L	20-50 micromoles/L
Theophylline	10-20 mg/L	50-110 micromoles/L

For gentamicin the purpose of TDM is to minimise the risk of nephrotoxicity and ototoxicity. The targeted trough drug concentration (<0.5 mg/L) is not a therapeutic range, but instead a range which is associated with minimal risk of toxicity. However achieving this target does not imply that an effective dose has been given as the bactericidal effect of aminoglycosides is related to peak concentrations.

Unless toxicity is suspected, TDM should be performed after sufficient time has elapsed to allow for a steady-state plasma concentration to be reached (i.e. the situation when drug intake equals drug clearance.) If loading doses have not been used this means waiting for a period of time approximating 4-5 half-lives of the drug after commencement of therapy or a dose change. Two exceptions to this are amiodarone and perhexiline which have very long half-lives and may be associated with serious toxicity, where dose adjustments may need to be made before steady state is reached.

In general blood samples for TDM should be trough samples i.e. the blood should be drawn just before the next scheduled dose. This is particularly important for drugs with a short half-life, such as theophylline or vancomycin. For drugs with a long half-life (> 24 hours) such as phenytoin or amiodarone there is less variation of drug concentration over the dosing interval and sampling time is therefore less critical. For digoxin blood samples should be drawn 6-24 hours after a dose to allow time for the drug to distribute into tissue during the first six hours.

Apart from dose, duration of therapy and time of sampling, there are many factors which need to be considered when applying TDM results in clinical practice. These include the patient's clinical condition, the indication for therapy, co-morbidities, medication adherence, and depending on the drug renal or hepatic function, protein binding, possible drug interactions and alcohol and tobacco use. “Treat the patient not the number” should be a guiding principle when using TDM results in clinical practice.

This E-Bulletin is based on work by Karin Nyfort-Hansen, Senior Clinical Pharmacist, RGH

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