Therapeutic Drug Monitoring

Some drugs have a narrow therapeutic index, which means that there is only a small difference between the minimum effective concentrations and the minimum toxic concentrations in the blood. With such drugs, small increases in dose or in blood/serum concentrations could lead to toxic effects. Therapeutic drug monitoring may help to optimise treatment in cases where there is a firm relationship between the toxic/therapeutic effects and drug concentrations in whole blood/serum.

A therapeutic interval has been defined for the drugs in the following tables. This is the minimum effective and maximum safe concentration for compliant patients, on stabilised regimens. Levels within these limits should prove satisfactory in most cases.

Whole blood or serum drug concentrations are useful for determining patient compliance or for assessing whether or not:

1. adequate concentrations are being achieved or,
2. potentially toxic concentrations are being reached.

Depending on clinical conditions, dosage adjustments may be needed when levels are outside the therapeutic interval. Therapeutic drug monitoring can also be useful when changes are made to other medications that could affect serum or whole blood concentrations and lead to a reduction in effectiveness or increased toxicity.

Although plasma drug concentrations and the therapeutic interval are useful in evaluating drug therapy, they should not be the only criteria on which treatment is based. Always remember to **treat the patient, not the level.**

Drug concentrations in serum or whole blood are only meaningful if the **correct procedures** are followed regarding the **timing** of specimens and selection of sample tube. **It is vitally important to note the exact time the sample is taken and when each dose of the drug is given.** (This is particularly relevant with the antibiotics eg gentamicin and vancomycin, see the Adult Antibiotic Policy.) This allows for accurate interpretation of the measured levels and the patient's response to their dosing regimen.

Some drugs need to be monitored at the "steady state" ie 4-5 half lives after initiation of therapy or a change in dosage. Care needs to be taken with loading doses eg digoxin and phenytoin where misleading concentrations may occur in the early stages of treatment if the timing of specimens is wrong. Failure to meet these requirements accounts for most errors in therapeutic drug monitoring.

Drugs for which the laboratories provide a routine monitoring service are listed in the table below together with details of specimen tubes and collecting times. It is possible to monitor other drugs and special arrangements can be made with the Department of Biochemical Medicine at Ninewells Hospital for certain pharmaceuticals. Throughout the Formulary and Antibiotic Policy, an indication is given when therapeutic monitoring is available for a listed drug. It is not essential that this is carried out in all cases but may be considered during the early treatment period if complications arise. Further information on laboratory services for therapeutic drug monitoring can be obtained from Departments of Biochemical Medicine and Medical Microbiology and further advice may be obtained from the clinical pharmacist at ward level or from the Medicines Information Service extn 32351.

DRUG	SPECIMEN	COLLECTION TIME	THERAPEUTIC INTERVAL	TIME TO STEADY STATE (days)
Carbamazepine	SST	Pre-dose	4-10 milligram/L	5
Ciclosporin	EDTA	Pre-dose	Therapeutic range depends on clinical situation (see below)	5
Digoxin*	SST	Pre-dose or at least 6 hours after the last dose	1.0 - 2.0 microgram/L	7
Lithium	SST	12 hours after the evening dose	0.4 - 0.8 millimol/L (prophylaxis) 0.8 - 1.2 millimol/L (mania)	4
Methotrexate	SST	24 and 48 hours post infusion	under 1 micromol/L at 48 hours	-
Phenobarbital**	SST	Anytime	10-40 milligram/L	20
Phenytoin***	SST	Anytime	10-20 milligram/L	Variable about 14 days
Tacrolimus	EDTA	Pre-dose	5 - 15 microgram/L	3
Theophylline	SST	Peak levels - 6 hours after sustained release dose. Trough levels - pre-dose	<4 years: 5-10 milligraml/L >4 years: 10-20 milligraml/L	2

* Potassium levels should be measured at the same time as diogoxin since this can alter the interpretation of the results
** Also used for monitoring primidone
*** Following fosphenytoin administration, there should be an interval of 4 hours before blood specimens are collected

THERAPEUTIC INTERVALS FOR CICLOSPORIN (microgram/L)
derived from EMIT figures in *TDM* 1995; 17: 642-54

TRANSPLANT	FIRST 6 MONTHS	AFTER 6 MONTHS
Kidney	125 - 200	75 - 150
Paediatric Kidney	150 - 250	100 - 150
Liver	125 - 200	75 - 150
Heart	275 - 375	150 - 250
Bone Marrow	95 - 204	95 - 204

Prepared by:
Dr S Jenner, Department of Biochemical Medicine