Guide to Therapeutic Drug Monitoring (TDM) for medications commonly used in aged care facilities

Therapeutic drug monitoring (TDM) involves measuring concentrations of a drug in plasma, serum or blood. It can be useful for:

- measuring effectiveness of a drug
- monitoring for toxicity
- measuring patient compliance/adherence to taking a drug
- diagnostic purposes.

However, it is not meaningful to monitor the concentration of every drug. For monitoring to be worthwhile, at least one of the following criteria should be met:

- Narrow target range/narrow therapeutic window
- Significant pharmacokinetic variability
- Reasonable relationship between plasma concentration and clinical effect
- Established target concentration range
- Availability of cost-effective drug assay.

Routine monitoring is not advocated for most drugs. Meaningful reasons for TDM include:

Toxicity

- To confirm toxicity if symptoms are ambiguous e.g.) if a patient on digoxin experiences nausea
- Avoiding toxicity

Dosing

- After dose adjustment
- To assess whether a loading dose (starting dose) was adequate e.g.) phenytoin

Monitoring

- Assessing adherence e.g.) if a person on a seizure medication continues to have ongoing seizures
- Diagnosing under-treatment
- Diagnosing failed therapy – to help distinguish between whether a dug is ineffective, the patient is non-adherent, or whether there are adverse effects which may mimic underlying disease.

When to monitor

- To ensure accurate result, the timing of the sample is important.
- The concentration prior to a drug dose (trough concentration) is usually used, as it represents the least variable point in the dosing interval, and therapeutic ranges have often been established this way. However, once the steady state level (where the drug concentration remains constant with ongoing dosing and normal elimination) is reached, for drugs which have a long half-life, the sample can be taken at any time.

Interpretation

As therapeutic ranges are usually taken from small studies, it is important to always interpret drug concentrations within the clinical context of the patient. It should also be noted that there may be variation between different laboratories.

Therapeutic ranges should only be used to guide dosage adjustments. However clinical response to therapy, symptoms and signs of toxicity, and adherence must be taken into account when interpreting results. Some people can have adverse effects at low concentrations, and others can tolerate high levels without adverse effects occurring. The elderly are generally more likely to be susceptible to adverse effects at lower concentration levels.

Anti-epileptic drugs

- Unfortunately, there is a poor link between the plasma concentration, and efficacy or toxicity of many anti-epileptic drugs. Despite this, therapeutic drug monitoring is still widely used in clinical practice. Studies indicate that errors occur frequently in relation to timing of blood taken and interpretation of drug levels.
- TDM is NOT recommended for gabapentin, topiramate, tiagabine, levetiracetam or vigabatrin.

There is also little evidence that the therapeutic ranges for epilepsy should be used for other indications e.g.) mood disorders, migraine prophylaxis.

- TDM can be useful however for phenytoin, carbamazepine and valproate.
- Specialists do use TDM for lamotrigine, however a definitive therapeutic range has not yet been established.
- Sodium valproate and phenytoin do not display linear pharmacokinetics. This means that making a change in the dose, results in a large and disproportionate change in plasma concentration. Therefore, making dose changes is complex.

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Special consideration – phenytoin

Most TDM involves measuring the total drug concentration (free unbound drug, and drug that is bound to protein). However, only the free unbound drug is active and interacts with receptors to produce a response. For phenytoin the total drug concentration can be a misleading result in certain circumstances:

- People with renal impairment
- People with low plasma albumin

These people may have an overall low total phenytoin level, HOWEVER, they may have a therapeutic level of free phenytoin. If there is no correction for albumin, this may be misinterpreted, and lead to an increase in phenytoin dose, and therefore toxicity.

Measurement of free phenytoin (unbound) is recommended for patients with low albumin or chronic renal failure.

Note: If this test is unavailable, the modified Sheiner-Tozer equation should be used to estimate the total phenytoin concentration that would be expected with a normal albumin concentration:

$$C_{normal} = \frac{C_{observed}}{0.02\ ALB + 0.1}$$

C observed = phenytoin concentration measured
ALB = serum albumin concentration in g/L
If CrCl < 10 mL/min, use 0.01 instead of 0.02 as multiplier in the equation.

Dose changes should also be conservative in these people.

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Medication	Therapeutic Range*	Half-life (hours)	Sampling Time**	Time to steady state (days)	Monitoring frequency	Some adverse effects	Other useful monitoring
Amiodarone	1-2.5 mg/L **(Little correlation between plasma concentration and efficacy or toxicity)**	14-59 **days** usual range (but can range from 14-110 days)	Can collect at any point as this drug has a long half-life	n/a	Routine monitoring is not recommended. **May** be used to assess for compliance.	Abnormal thyroid and liver function tests, bradycardia, nausea, anorexia, pulmonary toxicity, ocular effects, blue discoloration of skin, photosensitivity	• TFTs • LFTs • EUC • pulmonary function tests and chest X-ray • ophthalmic evaluation (if visual impairment or ocular symptoms occur)
Carbamazepine	4-12mg/L or 17-50 umol/L (Epilepsy only)	10-17	Trough	7-10	When clinically indicated (e.g. to assess for toxicity, increase in seizure frequency)	Electrolyte imbalance, central nervous system disturbances, visual disturbances, arrhythmia, conduction disturbances, gastrointestinal upset, rash	• FBC (risk of leucopenia, thrombocytopenia) **NOTE: Multiple potential drug-drug interactions may affect plasma concentrations
Clozapine	Clozapine: 350-370ng/mL (adverse effects more likely at > 600 ng/mL) Norclozapine (active metabolite): 100-600ng/mL	12 (ranges from 4-66)	Trough	n/a	6 monthly (more frequently if quitting smoking or starting interacting drugs)	Patients, prescribers and pharmacists must be registered with a Clozapine Monitoring Service due to the following potentially serious adverse effects: • neutropenia • agranulocytosis • myocarditis Others: cardiomyopathy, tachycardia, constipation, seizures, sedation, hypersalivation postural hypotension, weight gain, reflux	• FBC (white blood cell & neutrophil count) - weekly for first 18 weeks and 4 weekly thereafter (mandatory). • echocardiogram (6-12 monthly) • BGL • CRP (particularly during first 4 weeks) **NOTE: If abrupt cessation is necessary or occurs inadvertently, observe carefully for symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.
Cyclosporin **(Caution - Hazardous medication)**	50-125mcg/L (serum or plasma) 150-400mcg/L (whole blood)	5-18	Multiple samples refer to specialist unit	3-5	If attempting to avoid/ confirm toxicity	Nephrotoxicity, neurotoxicity, elevated ALTs, hypomagnesaemia, hyperkalaemia, hyperglycaemia, diarrhoea	• renal and hepatic function • lipids • electrolytes (particularly potassium) • FBC
Digoxin	0.5-0.8ug/L heart failure (0.64-0.96 nmol/L) Toxicity is more likely > 2 ug/L (2.56 nmol/L) but may occur at lower concentrations, particularly in the elderly or where there is electrolyte disturbance, renal impairment, hypoxia or hypothyroidism	36	Trough - take blood sample at least 6 hours post dose	7-10	When clinically indicated (e.g. to assess for potential toxicity when symptoms occur)	GI upset (nausea, diarrhoea), visual changes, electrolyte imbalance, central nervous system disturbances, arrhythmia, conduction disturbances, rash	• EUC • **NOTES: (1) Regularly assess for digoxin toxicity (including resting heart rate); routine measurement of pulse rate before giving next dose of digoxin is not necessary (2) In Atrial Fibrillation, use the lowest dose that alleviates symptoms rather than aiming for a specific concentration. Up to 0.9ug/L (1.15 nmol/L) may be acceptable in atrial fibrillation.
Flecainide	0.2-0.9mg/L	12-27	Trough	3-5	When clinically indicated	Nausea, vomiting diarrhoea, visual disturbances, tinnitus, tremor, paraesthesia, ataxia, worsening heart failure, angina, new or worsening arrhythmias	• EUC (particularly potassium)

NOTE: Refer to individual product information for complete details regarding appropriate monitoring and potential adverse effects.
*Therapeutic range may differ between laboratories. This reference must be used in conjunction with clinical judgement.
**trough – lowest concentration in the patient's blood stream. Taken prior to giving the next dose of the medication.

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Lamotrigine	3-14mg/L (Epilepsy only, **not well established**)	Approx. 25 (varies greatly from 14-59 hours)	Pre-dose trough	5 (longer if given with valproate)	May be useful to assess for toxicity	Dizziness, diplopia, ataxia, incoordination, confusion, gum hyperplasia, lymphadenopathy, hirsutism, osteomalacia, facial coarsening, skin rash, Stevens Johnson syndrome	**NOTE: Serious skin rash/reactions or hypersensitivity may occur – seek medical review
Lithium	0.6-1.2mmol/L (clinical toxicity can occur at lower concentrations) Acute mania: 0.8-1.2mmol/L Prophylaxis: 0.4-1.0mmol/L	8-55 (average 18-24)	Pre-dose trough (>12 hours after last dose)	3-7	3 monthly (*National Institute for Health and Care Excellence (NICE) Guidelines*)	Nausea, diarrhoea, vertigo, muscle weakness, tremor, fatigue, thirst, polyuria, leucocytosis, weight gain, oedema, hypothyroidism	• TFTs • Renal function • Serum calcium • PTH • EUC (particularly sodium) **NOTES: (1) Important to not exceed a level of 2 mmol/L however symptoms of toxicity may occur > 1.2 mmol/L in the elderly (2) Adequate sodium intake is essential + avoid excessive sweating – low sodium level can precipitate toxicity
Perhexiline	0.15-0.6ug/mL	7-14 **days**	Take sample 3-5 days after starting treatment to identify poor metabolisers. Then take samples regularly or as indicated.	14-30 days or longer	Monthly until stable within therapeutic range, then 3 monthly.	Ataxia, weight loss, peripheral neuropathy, hepatotoxicity	• LFTs • BGLs **NOTE: treatment should be reviewed/ discontinued if any of the following occur: - peripheral neuropathy - clinical signs of hepatic disease - persistent elevations of serum enzymes or abnormalities of LFTs - persistent/marked hypoglycaemia - excessive weight loss
Phenobarbitone	10-40mg/mL	90-100	Trough (however due to long half-life, can collect at any time once steady state is reached)	14-30	When clinically indicated	Sedation, depression, cognitive impairment, paradoxical insomnia, altered mood and behaviour, hyperactivity and aggression	
Phenytoin	Total phenytoin: 10-20mg/L Free phenytoin: 1-2mg/L	Approx. 24	Trough (any time once at steady state)	5-7	When clinically indicated – change in patient's condition which can alter pharmacokinetics (body weight changes, change in interacting drugs, change in liver or kidney function)	Dizziness, diplopia, ataxia, incoordination, confusion, gum hyperplasia, lymphadenopathy, hirsutism, osteomalacia, facial coarsening, skin rash, Stevens Johnson syndrome	• LFTs • FBC
Sodium Valproate	50-100mg/L (Epilepsy only)	15	Pre-dose trough	3-5	When clinically indicated	Ataxia, sedation, tremor, hepatotoxicity, thrombocytopenia, gastrointestinal irritation, weight gain, transient alopecia, hyperammonaemia	• FBC • LFTs

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