Therapeutic drug monitoring

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For full information on treatment side effects, cautions and contraindications, see electronic British National Formulary (www.bnf.org)

For information on preparing intravenous medicines for administration, see Medusa Injectable Medicines Guide for the NHS (see Clinical Guidance home page)

1. Introduction

Therapeutic Drug Monitoring aims to individualise drug therapy and avoid both sub-therapeutic and toxic plasma drug concentrations. A number of factors influence drug concentration and a single sample will only reflect the concentration at the sampling time.

When a new drug is introduced, 'steady state' will not be approached until four elimination half-lives have elapsed. Sampling prior to this time may not be beneficial unless a problem is anticipated (eg, non-compliance or toxicity). Results must be judged in light of clinical observations and other relevant investigations.

Clinical advice and assistance can be obtained from the laboratories performing the tests. Advice on drug dose selection and interpretation of measured plasma drug concentrations can be obtained from Clinical Pharmacists or the Pharmacy Department.

Exercise caution with obese individuals where drug dosing with water-soluble agents (such as gentamicin) should be based on ideal body weight.

Ideal body weight (IBW)
IBW Females = [45.5kg + (2.3 x every inch over 5ft)] kg
IBW Males = [50kg + (2.3 x every inch over 5ft)] kg

For Obese patients
Adjusted body weight = ideal body weight + 0.4 (actual body weight – ideal body weight)

Cockcroft and Gault equation for creatinine clearance

$$\text{Creatinine clearance (mL/min)} = \frac{Y \times (140 - \text{age}) \times \text{weight}}{\text{Serum creatinine umol/L}}$$

Where Y = 1.23 for males and 1.04 for females

The pharmacokinetic information provided in the following monographs relate to healthy adults unless otherwise specified. Information on paediatric and neonatal patients and in various clinical states can be provided on request from the Pharmacy Department.

Estimated glomerular filtration rate (eGFR)
Renal function is increasingly being reported on the basis of estimated Glomerular Filtration Rate (eGFR). eGFR estimates are reported in mL/min/1.73m2 . They are not the same as creatinine clearance estimates, which are reported in mL/min. eGFR estimates have not yet been validated for drug dosing. Dosing adjustment for renal impairment continues to be based on estimates of creatinine clearance (e.g. calculated from the Cockcroft and Gault equation or from a 24-hour urine collection).

2. Carbamazepine

Therapeutics	**Sampling**
Dosage forms: Oral, rectal. **Loading dose:** Not recommended. **Maintenance dose:** For epilepsy, initially 100 to 200mg bd orally increased gradually to a maximum of 1.6 to 2g/day. **Time to steady state:** More than 2 weeks when initiating therapy. **Therapeutic range:** 4 to 10mg/L. **Toxic effects:** Incoordination, blurred vision, diplopia, drowsiness, nystagmus, ataxia, arrhythmias, nausea and vomiting, diarrhoea, hyponatraemia.	**Volume of blood:** Fill to line. **Tube to use:** Ochre top. **Lab performing assay:** Wirral Clinical Biochemistry **Emergency service:** No, but urgent analysis may be arranged with the laboratory between 9am and 5pm. After 5pm analysis may be arranged through the laboratory on call biochemist. **Sampling times:** Trough level immediately before next dose. **Resampling time:** Do not resample within 1 week of change in dose unless question of compliance or toxicity. **Reporting procedure:** Available via PCIS
Pharmacokinetics	**Additional Information**
Elimination half-life: 30 to 35 hours after single dose. 15 to 20 hours after multiple (10 to 30) doses. **Major route of elimination:** 98% hepatic metabolism with some active metabolites. **Volume of distribution:** 0.8 to 1.9L/kg. **Factors affecting plasma concentration:** ***Increased*** in hepatic disease and by concurrent use with erythromycin, cimetidine, diltiazem, verapamil and isoniazid. ***Decreased*** by concurrent use with phenytoin or phenobarbital (phenobarbitone).	**1.** Carbamazepine induces its own metabolism. Consequently, although steady-state is achieved 2 to 3 weeks after initiating therapy, any change in dosage during chronic therapy will take approximately 1 week to produce a new steady state concentration. Carbamazepine will also induce the enzymes that metabolise many other drugs. **2.** Many drug interactions — check with a Pharmacist for detailed information. **3.** Requires careful plasma drug concentration monitoring during pregnancy. **4.** In general, the recommended rectal dose is 25% higher than the oral dose.

3. Ciclosporin

Therapeutics	**Sampling**
Dosage forms: Oral, intravenous infusion (over 2 to 6 hours). **Loading and maintenance doses:** Different doses are applicable for different clinical indications. Please refer to manufacturer Summary of Product Characteristics or Pharmacy Department for full details. **Time to steady state:** 72 hours. **Therapeutic range:** Depends on indication for treatment. **Toxic effects:** Nephrotoxicity, hepatotoxicity, muscle tremor, nausea, gingival hyperplasia, hypertension, hyperkalaemia.	**Volume of blood:** Fill to line. **Tube to use:** Lavender top. **Lab performing assay:** Referred out from Wirral Clinical Biochemistry. **Emergency service:** No. Samples taken outside hours should be sent to the laboratory. **Sampling time:** Trough level immediately before next dose; peak level not usually done for renal transplants. **Reporting procedure:** Available via PCIS.
Pharmacokinetics	**Additional Information**
Elimination half-life: 6 to 21 hours. **Major route of excretion:** Biliary. **Volume of distribution:** 3.9L/kg. **Factors affecting plasma concentration:** ***Increased*** by fluconazole, ketoconazole, itraconazole, erythromycin and verapamil. ***Decreased*** by hepatic enzyme inducers.	**1.** Dosage and plasma concentrations are variable depending on the type of transplant or other indication. **2.** Due to differences in bioavailability, the prescriber should specify the brand of ciclosporin. **3.** In general, the recommended intravenous dose is one third of the oral dose. **4.** The injection contains polyethoxylated castor oil that may lead to anaphylactic reactions when injected too rapidly.

4. Digoxin

Therapeutics	**Sampling**
Dosage forms: Oral, intravenous infusion. **Loading dose:** 750micrograms to 1.5mg orally in single or divided doses (6 hours apart) over 24 hours. Intravenous loading dose is not recommended, as the response is no more rapid than following oral administration. **Maintenance dose:** 62.5 to 500 micrograms daily (higher doses may be divided). **Time to steady state:** 1 week with normal renal function. **Therapeutic range:** 1 to 2 micrograms/L. **Toxic effects:** Nausea, vomiting, arrhythmias, visual disturbances, weakness and lethargy (noted >2 micrograms/L).	**Volume of blood:** Fill to line. **Tube to use:** Red top. **Lab performing assay:** Wirral Clinical Biochemistry **Sampling time:** Ideally trough sample taken immediately before next dose. Sample must be at least 6 hours after an oral dose and 4 to 6 hours after an intravenous dose. **Resampling time:** Within 24 hours of loading dose to confirm target concentration. After at least 1 week to assess maintenance dose. **Reporting procedure:** Available via PCIS.
Pharmacokinetics	**Additional Information**
Elimination half-life: 50 to 100 hours (normal renal function). Prolonged in renal failure. **Major route of excretion:** Mainly excreted unchanged in the urine. Hepatic metabolism to active metabolites. **Volume of distribution:** 7 to 8L/kg. **Factors affecting plasma concentration:** ***Increased*** in renal failure and hepatic disease and by concurrent use with amiodarone, diltiazem, verapamil, quinine, ciclosporin and possibly atorvastatin.	**1.** Dosage forms have different bioavailabilities hence the need to adjust dose accordingly. ♦ Intravenous bioavailability = 100% ♦ Tablet bioavailability = 50 to 90% ♦ Elixir bioavailability = 80% **2.** Electrolyte imbalance (decreased K+ and/or Mg2+ or raised Ca2+) can potentiate toxicity. Thyroid dysfunction may alter clinical response. **3.** Many drug interactions - contact the Pharmacy Department for detailed information

5. Gentamicin

Therapeutics	**Sampling**
Dosage forms: Slow intravenous bolus injection (over at least 3 minutes), intravenous infusion, intramuscular injection. **Loading dose:** 3mg/kg IBW. **Maintenance dose:** Contact the Pharmacy Department for individualised estimates. **Time to steady state:** 12 to 24 hours (depending on renal function). **Therapeutic range:** Peak 5 to 12mg/L, trough <2mg/L. **Toxic effects:** Ototoxicity (augmented by other ototoxic drugs — eg, intravenous frusemide), nephrotoxicity.	**Volume of blood:** Fill to line. **Tube to use:** Red top. **Lab performing assay:** Wirral Clinical Biochemistry **Emergency service:** Yes, but analysis of samples taken outside normal hours must be arranged with the on-call Biochemist and oncall Pharmacist. **Sampling times:** Two timed samples: 1 hour and 5 hours after a loading dose or as directed by the pharmacy department. Record the time the dose was given and the time the levels were taken on the request form. Measure trough sample immediately before next dose; peak sample 1 hour post-dose. **Resampling time:** Dependent on clinical status of the patient. As a guide; pre and post dose levels are usally checked twice weekly. **Reporting procedure:** Available via PCIS.
Pharmacokinetics	**Additional Information**
Elimination half-life: 2.5 to 4 hours (normal renal function). Prolonged in renal impairment. **Major route of elimination:** Renal excretion. **Volume of distribution:** 0.3L/kg. **Factors affecting plasma concentration:** ***Increased*** in renal impairment. ***Decreased*** in ascites, cystic fibrosis and sepsis.	**1.** Dosage is related to the severity of the infection, the age of the patient and the patient's renal function. **2.** Lower peak concentrations (5mg/L) may be acceptable in patients with urinary tract infections or endocarditis due to gram-positive bacteria.

6. Lithium

Therapeutics	**Sampling**
Dosage form: Oral. **Loading dose:** Not necessary. **Maintenance dose:** 500 to 1200mg/day. **Time to steady state:** 4 to 7 days. **Therapeutic range:** 0.4 to 1mmol/L. **Toxic effects:** Nausea, vomiting, diarrhoea, weight gain (these effects can occur within therapeutic range). Hand tremor, slurred speech, irritability, stupor, seizures, nephrotoxicity and increased reflexes.	**Volume of blood:** Fill to line. **Tube to use:** Red top. **Lab performing assay:** Wirral Clinical Biochemistry **Emergency service:** Yes. Contact the on-call Biochemist. **Sampling times:** 12 hours after previous dose. The time since the last dose should be stated. **Re-sample time:** When commencing therapy, or after a dose change concentrations should be checked after 4 to 5 days (never longer than 1 week), and thereafter every week until dosage has remained constant for 4 weeks and every 3 months thereafter. **Reporting procedure:** Available via PCIS. Results should be recorded in the patient's lithium monitoring book.
Pharmacokinetics	**Additional Information**
Elimination half-life: 18 to 36 hours. **Major route of elimination:** Freely filtered at glomerulus with 80% reabsorbed. No metabolism. **Volume of distribution:** 0.8L/kg. **Factors affecting plasma concentrations:** ***Increased*** in renal impairment, by diuretics, ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, hyponatraemia and intercurrent infection. ***Decreased*** by theophylline, acetazolamide and cisplatin.	**1.** Plasma concentrations should be checked if changing brand of lithium preparation. **2.** Many drug interactions. Contact the Pharmacy Department for detailed information. **3.** Close monitoring of perioperative fluid balance is important in patients taking lithium. **4.** Requirements of lithium monitoring are described in section 19 of the CNS section of the Medicines Formulary

7. Phenytoin

Therapeutics

Dosage form: Oral, slow intravenous injection (rate not exceeding 50mg/min).

Loading dose: 15mg/kg.

Maintenance dose: 200mg to 500mg daily adjusted according to clinical response and therapeutic drug monitoring. Start at 200mg daily in the elderly.

Time to steady state: 5 to 10 days.

Therapeutic range: 8 to15mg/L.

Toxic effects: Nystagmus, blurred vision, ataxia, drowsiness, ECG changes, seizures, coma.

Sampling

Volume of blood: Fill to line.

Tube to use: Red top.

Lab performing assay: Wirral Clinical Biochemistry.

Emergency service: Requests for analysis of samples taken outside normal hours must be arranged with the on-call Biochemist.

Sampling times: Trough sample immediately before next dose. Time since the last dose should be stated.

Resample time: Do not resample within 2 weeks of change in dose unless question of compliance or toxicity.

Reporting procedure: Available via PCIS.

Pharmacokinetics

Elimination half-life: 7 to 42 hours (increases with concentration).

Protein binding: 88 to 93%. To correct a phenytoin concentration for low albumin:

Equation 1) Use if CrCl >25mL/minute

$$\text{Corrected concentration} = \frac{\text{Observed concentration}}{(0.02 \times \text{albumin}) + 0.1}$$

Equation 2) Use if CrCl < 10mL/minute

$$\text{Corrected concentration} = \frac{\text{Observed concentration}}{(0.01 \times \text{albumin}) + 0.1}$$

Major route of elimination: Hepatic metabolism.

Factors affecting plasma concentration:
Increased in chronic hepatic failure and by concurrent administration with hepatic enzyme inhibitors.
Decreased in acute hepatitis and with concurrent administration of hepatic enzyme inducers.

Additional Information

1. Phenytoin is almost completely absorbed after oral administration, but the absorption rate is variable and prolonged after large doses. Absorption may be impaired by the concurrent administration of calcium salts, including nasogastric (NG) feeds. Stop NG feeds 2 hours before and for 2 hours after an oral dose.
2. Phenytoin is a hepatic enzyme inducer and can increase the metabolism of other drugs. Contact Pharmacy for further details.
3. Phenytoin undergoes dose-dependent elimination so increasing doses can cause disproportionately large increases in plasma concentration. Advise caution when increasing maintenance dose.
4. In end-stage renal failure, protein binding can be affected by low albumin and uraemia. In patients with CrCl 10 to 25mL/minute, binding is unpredictably altered and plasma concentrations can be difficult to interpret accurately. Contact Pharmacy for further advice.

8. Theophylline (aminophylline)

Therapeutics	**Sampling**
Dosage form: Oral theophylline and oral or intravenous aminophylline **Loading dose:** Intravenous aminophylline 5mg/kg over 20 minutes. This loading dose only applies to patients who have not received xanthines in the last 24 hours. **Maintenance dose:** Sustained release theophylline 175 to 500mg every 12 hours, intravenous aminophylline 500micrograms/kg/hour. **Time to steady state:** 3 days. **Therapeutic range:** 10 to 20mg/L. **Toxic effects:** Vomiting, nausea, restlessness, insomnia, serious arrhythmias, convulsions.	**Volume of blood:** Fill to line. **Tube to use:** Red top. **Lab performing assay:** Wirral Clinical Biochemistry **Emergency service:** Yes. **Sampling times:** After oral modified release preparations a trough sample should be taken immediately before the next dose. Time since last dose should be stated. Intravenous peak concentration 12 to 24 hours following start of maintenance infusion and then daily during maintenance treatment. **Resample time:** New steady state concentrations will be reached 48 hours after change in dose. **Reporting procedure:** Available via PCIS.
Pharmacokinetics	**Additional Information**
Elimination half-life: 8 to 24 hours. **Major route of elimination:** 90% hepatic, 10% renal. **Volume of distribution:** 0.5L/kg. **Factors affecting plasma concentration:** ***Increased*** by cardiac disease, hepatic disease or concurrent administration of hepatic enzyme inhibitors. ***Decreased*** by smoking and hepatic enzyme inducers.	**1.** Major adverse effects are not necessarily preceded by minor ones, so only plasma concentration measurements can be relied on to forewarn of impending serious toxicity. **2.** The brand of theophylline should not be changed without careful monitoring. **3.** Theophylline clearance is increased in hyperthyroidism and decreased in hypothyroidism. Plasma concentrations should be closely monitored.

9. Vancomycin

Therapeutics	**Sampling**
Dosage form: Intravenous infusion. **Loading dose:** See antiobiotic formulary **Maintenance dose:** See antiobiotic formulary **Time to steady state**: 32 hours. **Therapeutic range:** trough 5 to 15mg/L, up to 20mg/L in resistant infections. **Toxic effects:** Hypotension and anaphylactic reactions occur if given too quickly. Ototoxicity and nephrotoxicity are rare.	**Volume of blood:** Fill to line **Tube to use:** Red top. **Lab performing assay:** Wirral Clinical Biochemistry. **Emergency service:** Yes, but should not be necessary. **Sampling times:** The Pharmacy Department will advise on levels to be taken. Trough levels should be taken immediately before a dose. **Resample time:** Dependent on clinical status of patient, see page 156. In patients who require monitoring; as a guide; a trough level is usually taken on day 2 or 3 of therapy and repeated weekly. **Reporting procedure:** Available via PCIS.
Pharmacokinetics	**Additional Information**
Elimination half-life: 6 to 10 hours (normal renal function). Prolonged in renal impairment. **Major route of elimination:** 70 to 90% excreted unchanged in urine. **Volume of distribution:** 0.7L/kg. **Factors affecting plasma concentration:** ***Increased*** in renal impairment. ***Decreased*** in severe burns.	**1.** Vancomycin is administered by the intravenous route in the treatment of endocarditis and other serious infections caused by Gram-positive cocci including multi-resistant staphylococci. **2.** Peak levels are not usually required. If needed sample 2 hours after the end of the infusion. Range 18 to 36mg/L. **3.** Oral vancomycin is not absorbed but can be used for the treatment of pseudomembranous colitis due to *Clostridium difficile*. Monitoring is not required.