NHS Grampian

NHS Grampian Guideline For Therapeutic Drug Monitoring (TDM) In Adults

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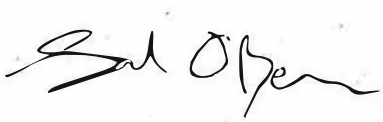
Signature: 	**Signature:** 	**Signature:** 

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Executive Sign-Off

This document has been endorsed by the Director of Pharmacy and Medicines Management

Signature: 

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Policy, Protocol, Procedure or Process Document:	Procedure
Document application:	NHS Grampian
Purpose/description:	To provide clear, concise guidance for medical, nursing and pharmacy staff about how to monitor drugs with a narrow therapeutic margin to ensure treatment is effective and safe.
Responsibility:	Responsibility for the effective management of the Acute Sector's policy, protocol, procedure and process documentation ultimately lies with the General Manager for the Acute Sector. Delegation for formulating, disseminating and controlling these documents falls to either a named individual or a working group.
Policy statement:	It is the responsibility of supervisory staff at all levels to ensure that their staff are working to the most up to date and relevant policies, protocols, and procedures. By doing so, the quality of the services offered will be maintained, and the chances of staff making erroneous decisions which may affect patient, staff or visitor safety and comfort will be reduced.

Responsibilities for ensuring registration of this document on the NHS Grampian Information/ Document Silo: Pharmacy and Medicines Directorate, Westholme

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Operational Management Unit: Unit Operational Managers
Departmental: Heads of Service/Clinical Leads
Area: Line Managers

Responsibilities for review of this document:
Lead Author/Co-ordinator: Medicines Information

Review date: This policy will be reviewed in three years or sooner if current treatment recommendations change.

Revision History:

Revision Date	Previous Revision Date	Summary of Changes (Descriptive summary of the changes made)	Changes Marked* (Identify page numbers and section heading)
Oct 2022	May 2019	Antibiotics removed from TDM guidance.	Throughout document
Oct 2022	May 2019	Updated frequency of tacrolimus and ciclosporin analysis.	P2
Oct 2022	May 2019	'Sample required' column removed from all monographs and link added to laboratory main tests page to supply this information.	Throughout document
Oct 2022	May 2019	Title of column 3 changed.	P3-6
Oct 2022	May 2019	Common signs and symptoms of toxicity – minor changes to entries for aminophylline, carbamazepine, ciclosporin, digoxin, lithium, phenobarbital, phenytoin, sodium valproate, tacrolimus.	Throughout document
Oct 2022	May 2019	Lower effective limit added to aminophylline, reduced sampling time.	P3
Oct 2022	May 2019	Additional monitoring information added to carbamazepine, ideal monitoring time amended.	P3

Revision Date	Previous Revision Date	Summary of Changes (Descriptive summary of the changes made)	Changes Marked* (Identify page numbers and section heading)
Oct 2022	May 2019	'In the absence of heart failure' added to comment on therapeutic range for digoxin and range extended.	P4
Oct 2022	May 2019	Link to national guidance document and SCA added to lithium.	P4
Oct 2022	May 2019	Additional comment added to therapeutic range and to optimal sampling time for IV administration for phenobarbital.	P5
Oct 2022	May 2019	Sodium valproate range amended in line with SPC.	P6
Oct 2022	May 2019	Theophylline sampling time clarified.	P6
Oct 2022	May 2019	Title amended to remove Acute Sector.	Title

NHS Grampian Guideline For Therapeutic Drug Monitoring (TDM) In Adults

Purpose

The aim of this guideline is to assist healthcare professionals with identifying therapeutic ranges, optimum sampling times, and signs of toxicity for medications that may require therapeutic drug monitoring (TDM), and to provide assistance with interpretation of results.

The aim of TDM is to provide information that assists in achieving rapid and optimum treatment. In general, routine drug monitoring is not required (exceptions: lithium, ciclosporin, IV aminophylline – see below) but rather are taken to resolve a specific clinical problem, e.g. inadequate response, signs of toxicity.

Please see separate guidance for therapeutic drug monitoring of antibiotics.

Considerations when reviewing TDM

When reviewing a drug monitoring result, the following must be considered to avoid misleading results:

1. For dosage adjustment guidance, sampling at 'steady-state' is essential (unless confirming toxicity) and thus at least four elimination half-lives must have elapsed since the last change of maintenance dose. Information in Table 1 below under the heading 'When to monitor after initiation or dose change' suggests the time to allow before sampling, based on the time it takes to achieve 'steady state', assuming no loading dose has been given.

   Note: Loading doses are sometimes given to allow 'steady state' levels to be achieved more rapidly. Following a maintenance dose increase, if levels are taken prior to steady-state being achieved, the drug concentration measured may still be sub-therapeutic. The resultant dose increase could result in toxic levels once steady state is reached.

2. Samples must be taken at an appropriate time during a dose interval. Interpretation of most results is made in relation to the therapeutic range but clinical decisions should not be based on drug concentrations alone and **full account must be taken of individual patient requirements and circumstances**. The range is only a guideline derived from a normal population and some patients will respond or exhibit toxicity outside the expected ranges. Drug levels can be affected by factors such as:
   - Age
   - Drug interactions
   - Protein binding
   - Drug metabolism
   - Liver and/or renal impairment may reduce clearance and increase the risk of toxicity, especially after a dose increase.
   - Time to steady state may be prolonged in some patients, e.g. the elderly, or those with renal or liver impairment.

3. Appropriate specimen collection time and documentation is vital. The request should indicate dose, times of doses and sampling time. Information on suspected non-compliance can be useful. See the Laboratories page for requirements on specimen containers.

Analysis of TDM

- Drug levels are analysed on a daily basis except for ciclosporin which are analysed on Tuesday and Friday.
- Results can be obtained electronically via TrakCare, SCI-store or Integrated Clinical Environment (ICE).
- Any enquiries regarding laboratory analysis can be obtained from Clinical Biochemistry on 51122.
- Help in interpretation of the results and dose adjustments for individual patients can be obtained from your Clinical Pharmacist, the Medicines Information Service (Ext 52316) or out of hours, from the On-call Pharmacist via switchboard.

Table 1

Medicine	Therapeutic range	When to monitor after initiation or dose change (assuming no loading dose given)	Optimum sampling time	Common signs and symptoms of toxicity
Aminophylline IV infusion	10 - 20mg/L (as theophylline) (5 - 15mg/L may be effective)	Daily	4 - 6 hours after starting infusion. Stop infusion for 15 minutes prior to sampling. (see local Respiratory protocol for more information).	Nausea, vomiting, restlessness, agitation, dilated pupils, tachycardia, arrhythmias, hyperglycaemia, hypokalaemia.
Carbamazepine	4 - 12mg/L Routine monitoring of plasma carbamazepine concentrations is not recommended; however, levels may be useful where the patient: • Experiences a loss of condition control • Becomes pregnant. • Has poor adherence. • Has suspected toxicity.	1 - 2 weeks after initiating treatment At least 4 days after a dose change in a patient on established therapy.	Pre-dose (trough).	Nausea, vomiting, dizziness, visual disturbances, drowsiness, arrhythmias, hyponatraemia, CNS depression, hallucination, agitation, retention of urine.

Medicine	Therapeutic range	When to monitor after initiation or dose change (assuming no loading dose given)	Optimum sampling time	Common signs and symptoms of toxicity
Ciclosporin	Varies with indication, seek specialist advice.	4 days	Oral: pre-dose (trough) IV: sampling time not critical.	Vomiting, drowsiness, headache, tachycardia, nephrotoxicity, hypertension.
Digoxin	0.5 - 1.0 micrograms/L **Note:** If being used for dysrhythmia in the absence of heart failure, a range of 0.5 – 2.0 micrograms/L may be appropriate, but ensure the patient is monitored for clinical signs of toxicity.	7 days	Pre-dose (trough) preferred but at least 6 hours after dose.	Anorexia, arrhythmias, vomiting, dizziness, diarrhoea, visual disturbances.
Lithium	Maintenance: 0.4 – 1.0mmol/L	5 - 7 days	12 hours after dose	Tremor, nausea, diarrhoea, ataxia, dysarthria, polyuria, confusion, blurred vision, nystagmus, muscle weakness, drowsiness. See local Shared Care Arrangement and national guidance document.

Medicine	Therapeutic range	When to monitor after initiation or dose change (assuming no loading dose given)	Optimum sampling time	Common signs and symptoms of toxicity
Phenobarbital (phenobarbitone)	10 - 40mg/L Monitoring plasma concentration may be less useful than with other medications as tolerance occurs.	14 days	Oral: Pre-dose (trough) preferred but sampling time not critical IV: Pre-dose (trough) preferred but sampling time not critical as long as it is at least 1 hour after the infusion ends	Drowsiness, nystagmus, ataxia, dysarthria, disinhibition.
Phenytoin **Note:** The interpretation of phenytoin levels in patients with low albumin requires an additional calculation.	5 - 20mg/L (see below).	Time to steady state can be prolonged. When initiating, sample at day 3, day 6 and day 13.	Oral: Pre-dose (trough) preferred but sampling time is not critical. IV: Pre-dose (trough)	Ataxia, slurred speech, nystagmus, confusion, hyperglycaemia.

Medicine	Therapeutic range	When to monitor after initiation or dose change (assuming no loading dose given)	Optimum sampling time	Common signs and symptoms of toxicity
Sodium Valproate	There is no meaningful reference range. Usually levels are used to confirm compliance only. Dose should be based on response. Typical levels may fall in the range 40 - 100mg/L in therapeutic use, but this should not be seen as a target range.	3 - 5 days	Pre-dose (trough).	Nausea, vomiting, dizziness, tremor, muscular hypotonia, hyporeflexia, miosis.
Tacrolimus	Varies with indication, seek specialist advice.	3 days after initiation. Sample 7 days after a dose change.	Pre-dose (trough).	Tremor, headache, nausea, vomiting, urticarial, lethargy, hypertension, infections.
Theophylline Oral	10 - 20mg/L	Sample 5 days after starting treatment, and 3 days after any dose adjustment.	Pre-dose (trough) or at least 6 hours post dose.	Nausea, vomiting, tachycardia, arrhythmias, haematemesis, hypotension, hypokalaemia, hypertonia, exaggerated limb reflexes, convulsions.

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   c) Neoral Soft Gelatin Capsules. Novartis Pharmaceuticals UK Ltd. Last updated 12 July 2022
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   e) Li-Liquid 1018 mg/5mL Oral Syrup. Rosemont Pharmaceuticals Limited. Last updated 1 June 2022
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   g) Phenytoin Sodium Flynn Hard Capsules 100mg. Flynn Pharma Ltd. Last updated 17 August 2022
   h) Epilim Chronosphere MR 250mg modified release granules. Sanofi. Last updated 19 August 2022
   i) Dailiport 5mg prolonged-release hard capsules. Sandoz Limited. Last updated 30 June 2022
   j) Uniphyllin Continus 200mg prolonged release tablets. Napp Pharmaceuticals Limited. Last updated 8 June 2021

Consultation List

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