East Kent Hospitals University NHS Foundation Trust

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Anti-Epileptic Drugs: Guidelines for requesting blood measurements

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Name of originator/author:	Dr Susan Vickery/Dr Edmund Lamb
Director responsible for implementation:	Dr Edmund Lamb (Consultant Clinical Scientist)
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Target audience:	Clinical staff (medical, nursing and scientific), Trust wide and primary care

Version Control

Version	Date	Author	Status	Comment
1.0	26-03-2013	Dr Susan Vickery Dr Edmund Lamb	archived	Broadened to include all AEDs (in addition to valproate). Revised to include recommendations from NICE Guidelines CG 137 2012
1.1	06-10-2013	Dr Susan Vickery Dr Edmund Lamb	archived	Broadened to be applicable to primary care following presentation at the East Kent Clinical Forum* on 3rd October 2013
1.2	23-08-2016	Dr Sally Stock	archived	Routine review
1.3	04-10-2019	Dr Sally Stock		Routine review, CG137 reviewed for updates. None that require inclusion in this guideline.
1.0	26-03-2013	Dr Susan Vickery Dr Edmund Lamb	archived	Broadened to include all AEDs (in addition to valproate). Revised to include recommendations from NICE Guidelines CG 137 2012
1.1	06-10-2013	Dr Susan Vickery Dr Edmund Lamb	archived	Broadened to be applicable to primary care following presentation at the East Kent Clinical Forum* on 3rd October 2013
1.2	23-08-2016	Dr Sally Stock	archived	Routine review, CG137 reviewed for updates. None that require inclusion in this guideline
2.0	23-05-2022	Miss Megan Manson/Dr S Stock		Document reformatted NICE guideline CG137 (January 2012) replaced with NICE guideline NG217 published 27-04-2022.

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Dr M Jenkinson (Lead Clinician Drugs and Therapeutics)	August 2022
Dr J Stanek (Consultant Paediatrician)	August 2022

Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Clinical Biochemistry Senior Staff	September 2022
Pathology Management and Governance Committee (PMGC)	October 2022
Clinical Support Services xx	October 2022

Contents

1. Introduction, Background and Purpose

This document gives advice on requesting anti-epileptic drug (AED) blood measurements in both adults and children. Epilepsy is a common neurological disorder characterised by recurring seizures. Different types of epilepsy have different causes. AEDs are used in both

adults and children to manage and control epilepsy. There is no evidence to support routine AED monitoring in adults or children. Blood test monitoring should only be done if clinically indicated.

2. Definitions

Anti-epileptic drug: medication taken daily to prevent the recurrence of epileptic seizures. Examples of anti-epileptic drugs: phenytoin, lamotrigine, sodium valproate, phenobarbital, carbamazepine, lamotrigine and levetiracetam.

3. Scope

This document outlines the clinical indications that support a request for AED blood measurement. It may be used for patients within the Trust and for requests arising in primary care.

4. Guidance

Routine monitoring of AED concentrations is NOT indicated in adults or children and should only be done if clinically indicated or in certain groups of patients (as defined below) (NICE Guideline 217 and Scottish Intercollegiate Guidelines Network (SIGN) guidelines 70 and 81) [1, 4, 5]). **Please ensure all requests are accompanied by relevant clinical information.**

There is no evidence to support routine AED monitoring in adults or children [1, 4, 5]. Evidence supports clinically useful dose-response and dose-toxic relationships for carbamazepine and phenytoin [4] Blood test monitoring should only be done if clinically indicated as described above [1, 4, 5].

Therapeutic drug monitoring of the AEDs such as phenytoin, lamotrigine, sodium valproate (Epilim™) phenobarbital, carbamazepine and levetiracetam should only be requested in the following situations/patients with:

1. Uncontrolled seizures
2. Suspected side effects from their medication
3. A specific clinical condition needing closer supervision (such as renal failure or during emergency treatment of convulsive status epilepticus or organ failure)
4. Poor adherence to prescribed medication (including compliance with treatment as part of safeguarding)
5. Suspected toxicity
6. Measurement may be useful in patients in whom there is particular difficulty in assessing the clinical response or calculating the dose. E.g. management of pharmacokinetic interactions causing changes in bioavailability, changes in elimination, and co-medication with interacting drugs.
7. In pregnancy if seizures increase or are likely to increase to aid increasing dose adjustments (refer to Epilepsy during Pregnancy Labour and the Puerperium, Women's Health, Policy Centre).

Measurement of phenytoin is indicated at initiation and adjustment of phenytoin concentration. (Trough phenytoin and albumin concentrations should be measured 18-24 hours following an i.v. loading dose and 2-3 days following initiation or dose change of oral therapy. Measurements should then be repeated 3-5 days later and continue to be measured weekly until stable. It may take up to 2 weeks to reach steady state.)

A **single measurement of lamotrigine** is indicated in women who may in the future become pregnant to provide a baseline measurement to guide management during pregnancy. Measurement should be made >2 weeks after commencing treatment to ensure steady state has been reached.

Measurement of sodium valproate may be indicated in the following circumstances:

(i) in patients receiving Epilim Chrono™ who have observed appearance of the drug in their stools and are concerned about lack of drug absorption.
(ii) in patients receiving Epilim for the treatment of bipolar affective disorder when the clinical response is inadequate.
(iii) in patients receiving Epilim Intravenous™.

For serum valproate, a useful concentration-effect relationship has never been demonstrated. The actions of sodium valproate are longer lasting than can be explained by the pharmacokinetics of the drug [1]. Variations in protein binding of valproate, for example in hepatic and renal disease and pregnancy, complicate the interpretation of serum valproate concentrations: measurement of salivary valproate will not compensate for these effects [2]. Serum valproate concentrations are no better a guide to clinical response than the dose. Patients should be monitored on the basis of clinical response. Routine monitoring of serum concentrations is unjustified [1, 4, 6]. The concentration-toxicity relationship is less clear for valproate than for many other drugs: there is wide variation in individual tolerability [1-2].

The therapeutic range for serum valproate is not well validated [2]. A tentative target range of 50-100 mg/L is commonly used. Some patients may require concentrations in excess of 100 mg/L before control is achieved whilst in others adverse effects may occur at concentrations below 100 mg/L. Conversely, some patients may achieve adequate control with serum concentrations below 50 mg/L. In patients who are resistant to treatment, serum valproate concentrations in excess of 150 mg/L suggest that an alternative therapeutic agent should be tried [1].

Sample requirements

In cases where measurement of an AED concentration is indicated for therapeutic monitoring, ideally a **pre-dose (trough) sample should be collected (after achieving steady-state) into a plain (red-top) blood collection tube**. [1].

Certain drugs will bind to the separating gel found in gel separator tube (GST, yellow-top) vacutainers, resulting in falsely low concentrations [3]. Blood samples for therapeutic drug monitoring of AEDs must be taken into plain (red top) vacutainers

5. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guideline

Consultation has been through e-mail communication between clinical biochemistry staff and Dr Mike Jenkinson, Dr Jan Stanek.

6. Review and Revision Arrangements

Two years from implementation date, by author.

7. Training

Trust Net under Clinical Biochemistry guidelines, by awareness raising through TrustNews, by proactive implementation through the Care Groups by appropriate clinical leads and by proactive dissemination to primary care partners (e.g. through newsletters, feedback on test requests and through electronic alert comments on requesting systems).Information is also hosted on the Pathology MicroGuide.

8. Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

9. Monitoring

Within the Trust, compliance with this guideline must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

10. References and Associated Documents

1. Epilepsies in children, young people and adults. NICE guideline [NG217]. https://www.nice.org.uk/guidance/ng217
2. Hallworth M, Capps N. Therapeutic Drug Monitoring. ACB Venture Publications 1993.
3. Bergqvist Y, Eckerbom S, Funding L. Effect of gel-barrier sampling tubes on determination of some antiepileptic drugs in serum. Clin Chem 1984; 30:465-6
4. Scottish Intercollegiate Guidelines Network (SIGN) guideline 70 (October 2005) – Diagnosis and management of epilepsy in adults.
5. Scottish Intercollegiate Guidelines Network (SIGN) guideline 81 (October 2005) – Diagnosis and management of epilepsy in children.
6. Valproate. BNF 65, March-Sept 2013, page 302.