ANTI-EPILEPTIC DRUGS: GUIDELINES FOR REQUESTING BLOOD MEASUREMENTS

Version:	1.3
Ratified by:	Clinical Biochemistry Senior Staff Group
Date ratified:	16th May 2013
Name of originator/author:	Dr Susan Vickery/Dr Edmund Lamb
Director responsible for implementation:	Mrs Ruth Lapworth
Date issued:	4 October 2019
Review date:	3 years after date issued
Target audience:	Clinical staff (medical, nursing and scientific), Trust wide ,East Kent Primary Care

Version Control Schedule

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.

Contents

1 Policy Summary

This policy gives guidance on requesting anti-epileptic drug (AED) blood measurements in both adults and children.

2 Introduction

Epilepsy is a common neurological disorder characterised by recurring seizures and 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.

3 Purpose and Scope

This policy 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 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 and levetiracetam.

5 Duties

All staff involved in the requesting of AED blood measurements, whether clinical or laboratory, must adhere to this policy.

6 Anti-epileptic drugs: guidelines for requesting blood measurements

Routine monitoring of AED concentrations is NOT indicated in adults or children and should only be done if clinically indicated (NICE Clinical Guideline 137 and Scottish Intercollegiate Guidelines Network (SIGN) guidelines 70 and 81) [1,4-5]. **Please phone the Duty Biochemist (ext 86287) to discuss prior to collecting samples: if measurement is indicated please ensure all clinical details accompany request.**

AEDs such as phenytoin, lamotrigine, sodium valproate (Epilim™) phenobarbital, carbamazepine and levetiracetam should only be requested in the following situations:

1. Detection of non-adherence to the prescribed medication.
2. Suspected toxicity.

3. Initiation and adjustment of phenytoin concentration. (Trough phenytoin and albumin levels should be measured 18-24 hours following an i.v. loading dose and 2 -3 days following initiation or dose change of oral therapy. Levels should then be repeated 3 -5 days later and continue to measure weekly until stable. It may take up to 2 weeks to reach steady state.)
4. 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).
5. Specific clinical conditions, e.g. during emergency treatment of convulsive status epilepticus or organ failure.
6. In pregnancy if seizures increase or are likely to increase to aid increasing dose adjustments (refer to Epilepsy during Pregnancy Labour and the Puerperium, Directorate of Women's Health).

In addition 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.

In addition **measurement of sodium valproate** may be indicated in the following circumstances:
(i) Measurement may be useful in patients receiving Epilim Chrono™ who have observed appearance of the drug in their stools and are concerned about lack of drug absorption.
(ii) Measurement may be useful in patients receiving Epilim for the treatment of bipolar affective disorder when the clinical response is inadequate.
(iii) Measurement may be useful in patients receiving Epilim Intravenous™.

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**. In adults, liver function tests should be monitored every 2 to 5 years for those patients taking enzyme-inducing AEDs [1].

Rationale for the guidelines

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].

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 serum 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].

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

7 Key Stakeholders, Consultation, Approval and Ratification Process

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

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff, Trust consultant neurologist (Dr N Moran), Trust consultant paediatrician (Dr A Siddiqui), Lead Clinician Drugs and Therapeutics (Dr M Jenkinson), Trust neurology pharmacist (Karen Bartlett) and Divisional Medical Director Urgent and Long-Term Conditions (Dr A Heller). Copies of correspondence are held on the T-drive; communication with users/clinical guidelines/AED. The policy was presented at and approved by the East Kent Clinical Forum on 3rd October 2013.

8 Review and Revision Arrangements

Three years from implementation date, by author.

9 Dissemination and Implementation

Trust Net under Clinical Biochemistry guidelines, by awareness raising through TrustNews, by proactive implementation through the Divisions 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).

10 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

11 Monitoring Compliance

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

12 References

1. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE Clinical Guideline 137 http://guidance.nice.org.uk/CG137
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.

13 Associated Documentation

Not applicable

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Anti-epileptic drugs: Guidelines for requesting blood measurements

Details of person completing the EHRIA	
Name	Dr Susan Vickery
Job Title	Senior Clinical Scientist
Department/Specialty	Laboratory Medicine/Clinical Biochemistry
Telephone Number	ext 86165

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate requesting of anti-epileptic drug blood measurements across the health service in East Kent.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Dr Susan Vickery, Senior Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr Edmund Lamb, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	

Appendix C – Plan for Dissemination of Policies

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

Acknowledgement: University Hospitals of Leicester NHS Trust (Amended)

Title of document:	Anti-epileptic drugs: Guidelines for requesting blood measurements		
Version Number:	1.0		
Approval Date:	03-10-2013	**Dissemination lead:**	Dr Susan Vickery
Previous document already being used?	Yes		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	clinical biochemistry guideline area in the GP zone on TrustNet (www.ekhuft.nhs.uk/clinicalbiochemistry)		
Proposed instructions regarding previous document:	This version will replace version 3.0 which will be withdrawn.		

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Format (i.e. paper or electronic)**	**Comments:**
Trust clinical staff	TrustNet	electronic	
Primary care	Newsletters, in the clinical biochemistry guideline area in the GP zone on TrustNet (www.ekhuft.nhs.uk/clinicalbiochemistry) and in the future hosted on Kent Pathology Partnership website	electronic	
Clinical Biochemistry staff	SharePoint/Q-Pulse	electronic	Existence of revised policy to be highlighted at staff meetings.

Author's Dissemination Record - to be used once document is approved – to be kept with the master document

Date document forwarded to be put on the Trust's central register / in SharePoint:		**Date document put on Directorate register (if appropriate) / on Directorate webpage (if applicable)**	

Disseminated to: (either directly or via meetings, etc.)	By Whom?	Format (i.e. paper or electronic)	Date Disseminated:
Clinical Scientists, East Kent at journal club meeting	EJL/SV	Presentation	3rd October 2013
Trust-wide through TrustNews article	SV	TrustNews	11th October 2013