The influence of oral contraceptives on lamotrigine clearance in patients on lamotrigine in combination with valproic acid, carbamazepine or oxcarbazepine as compared to patients on lamotrigine only.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON32536

Source
ToetsingOnline

Brief title
ltg/oc in combination therapy

Condition

- Neurological disorders NEC

Synonym
epilepsy

Research involving

Human

Sponsors and support

Primary sponsor: Stichting Epilepsie Instellingen Nederland
Source(s) of monetary or material Support: Christelijke vereniging voor de verpleging van lijders aan epiepsie.

Intervention

Keyword: combination therapy, lamotrigine, oral contraceptives, pharmacokinetics

Outcome measures

Primary outcome

LTG serum levels as well as serum levels of VPA, or CBZ or OCB during the

cycles will be primary study parameters.

Secondary outcome

seizures and side effects will be secundary parameters.

Study description

Background summary

Lamotrigine (LTG) is an anticonvulsant drug that is widely used in the treatment of epilepsy in all age groups. A pharmacokinetic interaction between LTG and combined oral contraceptives (OCs) was demonstrated in two small retrospective studies(1,2), in a double-blind placebo controlled trial(3) and in our previous study(4). In these studies, the use of OCs resulted in a 50% reduction of the plasma level of LTG. Changes in plasma levels of LTG could have a significant clinical relevance either by recurrence of seizures, increased seizure frequency or by an increased frequency of adverse effects. The changes in LTG clearance during OC use are probably due to steroid induction of hepatic 2-N-glucuronidation, which is the major route of metabolism for LTG. The pathway of glucuronidation is inhibited by the anticonvulsant drug valproic acid (VPA) and is induced by enzyme inducing drugs (e.g. rifampicine and enzyme inducing anticonvulsants)(5). OCs are also able to induce glucuronide conjugating enzymes(6).
References
1. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels

reduced by oral contraceptives. Epilepsy Res 2001;47:151-154.
2. Sabers A, Öhman I, Christensen J, Tomson T. Oral contraceptives reduce lamotrigine plasma levels. Neurology 2003;61:570-571.
3. Christensen J, Petrenaite V, Atterman J, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. Epilepsia 2007;48(3):484-489.
4. Wegner I, Edelbroek PM, Bulk S, Lindhout D. Lamotrigine kinetics within the menstrual cycle, postmenopausal and with oral contraceptives. Neurology in press.
5. Dickins M, Chen C. Lamotrigine. Chemistry, biotransformation, and pharmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, editors. Antiepileptic drugs, 5th ed. Lippincott Williams and Wilkins;2002:370-379.
6. Shenfield GM, Griffin JM. Clinical pharmacokinetics of contraceptive steroids. An update. Clin Pharmacokinet 1991; 20 (1):15-37.

Study objective

In a previous prospective study(4), we investigated in detail the effect of OCs on LTG clearance. However, LTG is frequently used in combination therapy. This raises the question as to what extent and how co-medication with other anti-epileptic drugs like VPA may alter the pharmacokinetic interaction between LTG and OC. In this new prospective study we aim to analyse the effects of frequently used comedication (VPA, carbamazepine (CBZ) and oxcarbazepine (OCB)) on the interference of OC hormones on LTG metabolism.

Study design

In an open, prospective study we will select women in the age of 18-40 years that use OC in a stable dose as well as a stable dose of 1)LTG and VPA, 2)LTG and CBZ, 3)LTG and OCB. In each woman we will study two consecutive cycles starting with the first pill of a strip of OCs. Every other day serum levels of the AEDs will be assessed, using a dried bloodspot method. At home, women will obtain a finger puncture blood drop using an automatic disposable lancet, which is then applied to a standardized filter paper. Samples will be sent to our laboratory where they will be analysed.

Study burden and risks

There is no intervention.
There is no risk for the patient participating in this study.
The burden for the patient will be to obtain at home a finger puncture blood drop every other day during a period of 8 weeks, using an automatic disposable lancet.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

women in the age of 18-40 years that use OC in a stable dose as well as a stable dose of 1)LTG and VPA, 2)LTG and CBZ, 3)LTG and OCB.

Exclusion criteria

Use of steroid hormones (other than OC) as well as pregnancy or the intention to conceive, current breastfeeding or having delivered in the nine months prior to the study. Patients with abnormal liver and/or renal function or with known gynaecological or psychiatric co morbidity will be excluded.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-02-2010
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	lamictal
Generic name:	lamotrigine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	22-10-2009
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	26-10-2009
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015701-39-NL
CCMO	NL29378.058.09