Potential interaction between lamotrigine and estradiol/dydrogesteron leading to decreased lamotrigine blood levels

Introduction

Lamotrigine (Lamictal®) is an antiepileptic indicated for the treatment (monotherapy or adjunctive therapy) of *partial epilepsy* and *generalized epilepsy* and for the treatment (initial therapy or adjunctive therapy) of *syndrome of Lennox-Gastaut* in adults and children older than 12 years. In addition, in children aged 2-12 years, the drug is indicated as adjunctive therapy for the treatment of partial epilepsy and generalized epilepsy, as adjunctive therapy for the treatment of syndrome of Lennox-Gastaut and as monotherapy for the treatment of absence epilepsy. Furthermore, lamotrigine is indicated in adults for the *prophylaxis of depressive episodes* in patients with bipolar disorder [1]. Lamotrigine was granted market authorisation in the Netherlands in 1996 (Lamictal®) [1]. Lamotrigine is a use- and voltage-dependent blocker of voltage gated sodium channels. It inhibits sustained repetitive firing of neurones and inhibits release of glutamate [2].

Estradiol/dydrogesteron (Femoston® or Femoston continu®) is indicated as *hormone replacement therapy (HRT) for estrogen deficiency symptoms* in women who are in the menopause for at least 6 months (Femoston®) or for at least 12 months (Femoston continu®). Also, it is indicated for the *prevention of postmenopausal osteoporosis* in women with a high risk of future fractures and who do not tolerate or have a contra-indication for other products approved for the prevention of osteoporosis [3,4]. The product Femoston® consists of 14 tablets only containing estradiol and 14 tablets containing estradiol and dydrogesteron. The product Femoston continu® consists of 28 tablets containing estradiol and dydrogesteron. The products contain synthetic 17β-oestradiol, which is chemically and biologically identical to endogenous human estradiol. Dydrogesterone is an orally-active progestogen having an activity comparable to parenterally administered progesterone [5]. Femoston® was granted market authorisation in the Netherlands in 1995, Femoston continu® was granted market authorisation in the Netherlands in 2000 [3,4].

Reports

In September 2022 the Netherlands Pharmacovigilance Centre Lareb received 1 report of a possible interaction between lamotrigine and estradiol/dydrogesteron, which probably led to decreased lamotrigine blood levels. The report came from a consumer who experienced this herself.
At the time of writing this signal (January 2023), this report is the only one about an interaction between lamotrigine and estradiol/dydrogesteron in the Lareb database. It's also the only one about an interaction between lamotrigine and HRT.

Case A (NL-LRB-00829173)
The case report concerns a 50-60 year-old woman who since teenage age has recurrent depressive episodes alternating with good periods. In the past she has used several antidepressants which weren't effective enough. Since 2015 the recurrent depressive episodes were well-controlled with lamotrigine. At the time of reporting (September 2022) she indicated that she never had such a long period without depression.
In February 2022 she started using estradiol/dydrogesteron tablets (Femoston 1/10®) for menopausal symptoms. About 5 months later she felt like she was slipping back into depression again.
On an English website she read about a drug-drug interaction between estradiol/dydrogesteron and lamotrigine [6]. After that she contacted the general practitioner. The blood level of lamotrigine was measured and was 2.9 mg/l (this was 29 weeks after the start of estradiol/dydrogesteron). The specific details of the measurement (like collection time) were not indicated. The patient indicated that she doesn't know her blood levels of lamotrigine before the use of estradiol/dydrogesteron. The therapeutic range for bipolar disorder is 5-11 mg/l [7]. Although there is also literature suggesting that lower levels can be effective for mood disorders [8].

It was decided to discontinue the use of estradiol/dydrogesteron. The patient indicated that a tapering protocol was needed for this. Her usual dosage of lamotrigine of 200 mg per day was tapered to 150 mg per day for 5 days. Then it was tapered to 100 mg per day for 10 days. In the

middle of this period the estradiol/dydrogesteron was withdrawn. Then the dosage of lamotrigine was built up again to 150 mg per day for 5 days after which the dosage was increased back to her usual daily dosage of 200 mg.
Her lamotrigine blood level was measured three weeks after she returned to her usual daily dosage of 200 mg of lamotrigine (which was 4.5 weeks after stopping the estradiol/dydrogesteron). The lamotrigine blood level was 5.3 mg/l.
About 6 weeks after the patient is back on her usual daily dosage of lamotrigine (which is about 7.5 weeks after stopping the estradiol/dydrogesteron) the patient indicated that she is recovering from the complaints (depression). She describes that slowly she feels like she is on the way up again. She indicated that it's difficult to say when she started to feel better because many factors play a role and it's not one way up (or down). She can remember that she had a bad period of time (again) when she was reducing and increasing the lamotrigine dosage.

Other Sources of information

SmPC
The SmPC of lamotrigine contains a paragraph about interactions with hormonal contraceptives in section '4.5. Interactions with other medicinal products and other forms of interaction'. Also, section '4.4 Special warnings and precautions for use' contains a paragraph with information about interactions with hormonal contraceptives. The paragraph in section 4.4 also contains a warning about hormone replacement therapies [1]. The text in the paragraph is as follows:
"*Effects of hormonal contraception on lamotrigine efficacy*
A combination of ethinylestradiol/levonorgestrel (30 mcg/150 mcg) has been shown to increase the clearance of lamotrigine approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A reduction in lamotrigine levels was associated with loss of seizure control. Following lamotrigine initiation, in most cases a higher maintenance dose of lamotrigine will be required (up to a factor of two) to achieve maximum therapeutic response. When oral contraceptives are discontinued, the clearance of lamotrigine may be reduced by half. Increases in lamotrigine concentrations may be associated with dose-related side effects. The patient should be monitored for this. In women who are not taking an inducer of lamotrigine glucuronidation and are using hormonal contraception that includes a week of inactive medication (e.g., a pill-free week), gradual, transient increases in their lamotrigine levels may occur during the week of inactive medication (see section 4.2). Such changes in lamotrigine levels may be associated with side effects. Therefore, contraception without a pill-free week (e.g. a continuous hormonal contraceptive or non-hormonal methods) should be considered as first-line treatment.
The interaction between other oral contraceptives or hormone replacement therapies (HRT) and lamotrigine has not been studied, but they may exert a similar effect on the pharmacokinetics of lamotrigine." [1]

Both the SmPC of Femoston 1/10® as well as Femoston continu 1/5® contain no information about a possible interaction with lamotrigine. Section 4.5 mentions a possible interaction with anticonvulsants (lamotrigine is not specifically mentioned), but this concerns the efficacy of estrogens and progestogens. The underlying mechanism for this interaction is induction of P450 enzymes [3,4]. The text about this interaction is as follows:
"The metabolism of estrogens (and progestogens) may increase with concomitant use of substances known to induce enzymes involved in the drug metabolism. This is especially true for P450 enzymes. Among these substances are anticonvulsants (phenobarbital, phenytoin, carbamazepine) and antibacterial/antiviral agents (e.g. rifampicin, rifabutin, nevirapine, efavirenz)." [3,4]

Only the SmPC's of the estradiol containing products below contain information about lamotrigine [9]:
1. Nomegestrolacetaat/Estradiol Viatris 2,5 mg/1,5 mg tablets
2. Qlaira filmomhulde tabletten (containing estradiolvaleraat and/or dienogest)
3. Zoanne 2,5 mg/1,5 mg tablets (containing nomegestrol acetate and estradiol hemihydrate)
4. Bijuva 1 mg/100 mg capsules (containing 1 mg oestradiol and 100 mg progesteron)

These first three products are indicated for oral contraception. Only Bijuva® is indicated for HRT in postmenopausal women. The SmPC of Bijuva® contains the following information in section 4.5:

" Hormonal contraceptives containing estrogens have been shown to decrease the plasma concentration of lamotrigine significantly when co-administered, due to induction of lamotrigine glucuronidation. This can weaken seizure control. Although the possible interaction between hormone replacement therapy and lamotrigine was not studied, a similar interaction is expected, which may lead to a decrease in seizure control in women taking both drugs together."[10]

Literature

Influence of other HRT on lamotrigine concentration

Harden et al. performed a randomized, double blind, placebo-controlled trial about the effect of HRT on seizure frequency in postmenopausal women with epilepsy, who were taking stable doses of antiepileptic drugs (several types) and who were within 10 years of their last menses. The HRT in this study was Prempro® which is 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate, designated here as CEE/MPA. A dose effect of CEE/MPA on seizure frequency was assessed by using two doses: a single and a double dose. In total 21 subjects were randomized in this study: 6 in the placebo group, 8 in the single dose CEE/MPA group and 7 in the double dose CEE/MPA group.
In the two subjects randomized to CEE/MPA who also were taking lamotrigine, a consistent directional change was found. In one subject receiving polytherapy, lamotrigine levels declined from a mean of 9.6 µg/ml (range, 10.1–9.2) during baseline, to a mean of 7.7 µg/ml (range, 6.4–8) during treatment, with no change in seizures. In another subject receiving monotherapy, the lamotrigine levels declined from a mean of 2.1 µg/ml (range, 2.6–1.5) during baseline to a mean of 1.4 µg/ml (range,1.3–1.5) during treatment, and this subject did have increased seizures during treatment. Therefore lamotrigine levels declined by 25–30% in these subjects. Both subjects were in the single-dose CEE/MPA treatment arm [11].
In 2016 Reimers et al. performed a matched case-control study exploring the possibility of a drug interaction between lamotrigine and estrogens used for HRT [12]. Data from serum samples analyzed for lamotrigine were retrieved from a routine therapeutic drug monitoring database. Users of HRT and ethinylestradiol (EE) were identified and matched with controls for age and dose. No enzyme-inducing or enzyme-inhibiting comedication was allowed. Lamotrigine serum concentration-to-dose ratios (CDRs) were calculated. Seventy-nine HRT users (dose range 1–4 mg/day) and 200 EE users (dose range 20–40 µg/day), as well as 158 and 400 matching controls, respectively, were included. Both EE users and HRT users had significantly lower mean lamotrigine CDRs than their respective matched controls. Of the HRT users in this study 85% used estradiol and 15% used estriol [13].

Lamotrigine clearance in post-menopausal women

Some studies are available about the pharmacokinetics of lamotrigine in post-menopausal women. The results of these studies are conflicting [13]. Post-menopausal age itself has been associated with unaltered, increased, and reduced lamotrigine clearance [14,15,16]. According to Reimers et al. the results of these studies are difficult to interpret and compare due to differences in study size, study design and whether the use of HRT was taken into account [13].

Influence of estradiol on lamotrigine concentration

Several studies have shown that lamotrigine clearance may increase by 65—230% during gestation. Accordingly, serum concentrations may decrease by more than 60%, often requiring dose adjustments. These pharmacokinetic changes are subject to marked interindividual variability. Serum concentrations return to pre-pregnancy values within 2-3 weeks postpartum [12].
Human pregnancy is accompanied by various physiological changes, including a dramatic increase in the production of female hormones, i.e., estrogen and progesterone. Blood levels of these hormones rise up to 100-fold by term. At this high concentration, female hormones manifest functions different from those of their conventional role as gonadal hormones. Clinical evidence suggests that pregnancy also alters the rate and extent of hepatic drug metabolism [17].
Chen at al. used liver cells (HepG2 cells) to study the mechanism in which the clearance of lamotrigine is increased in pregnancy. Their results suggest that elevated levels of 17β-Estradiol (E_2), the major estrogen in humans, is responsible for increased clearance of lamotrigine [17]. This mechanism will be explained in more detail below.

Monitoring in pharmacovigilance systems
Stichting Health Base (SHB) monitors an interaction between lamotrigine and all systemic estrogens in their medication monitoring system. Although they indicate that a decrease in the plasma level of lamotrigine is only demonstrated in users of ethinylestradiol, they do state that it's likely that all estrogens can decrease the plasma levels of lamotrigine. For this they refer to the decrease in lamotrigine levels during pregnancy, which is probably related to higher concentrations of estradiol [18].
Stockley's Drug Interactions also warns of an interaction between lamotrigine and HRT [19].
The Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP) does not monitor an interaction between lamotrigine and all systemic estrogens. But they do monitor the interaction between lamotrigine and hormonal contraceptives. This monitoring also includes hormonal contraceptives that contain another estrogenic component than ethinylestradiol (such as estradiol/dienogest and estradiol/nomegestrol) [20].

Mechanism
Lamotrigine is rapidly and completely absorbed from the intestine and undergoes extensive metabolism by UDP-glucuronosyltransferase (UGT) 1A4 and UGT2B7, with minimal renal excretion [17]. Via isoenzyme UGT1A4 lamotrigine is metabolized to an inactive 2-N-glucuronide (2-NGLUC) [21]. 17β-Estradiol (E_2), the major estrogen in humans, has been shown to activate UGT1A4 expression. This probably contributes to altered metabolism of UGT1A4 substrate drugs in pregnancy and provide a potential mechanistic basis for the increased lamotrigine clearance in pregnancy and in oral contraceptive users [17].

Discussion and conclusion

The report Lareb received (case A) describes a menopausal woman with a history of recurrent depression who has been stable on lamotrigine for many years. The recurrent depression which she describes in the report, could also be caused by the menopause itself or by a side effect of the progestagen in the HRT she is being treated with. It is known that the menopause itself can cause depression [22]. Also its known that progestogens itself can cause depression [23]. The SmPC of estradiol/dydrogesteron (Femoston® or Femoston continu®) lists depression as a side effect with a frequency of ≥1/100, <1/10 [3,4]. However, the values of the measured lamotrigine levels in the case (during and after discontinuation of estradiol/dydrogesterone) suggest that the lamotrigine level in this patient played a role in the development of the depressive symptoms. During the use of estradiol/dydrogesteron the lamotrigine level of the patient was remarkably lower than after withdrawal of estradiol/dydrogesteron. These findings support a possible interaction between lamotrigine and estradiol/dydrogesteron.

There are no studies available concerning a drug interaction between lamotrigine and estradiol/dydrogesteron. However, studies on drug interaction between combined oral contraceptives and lamotrigine showed a reduction of the lamotrigine serum concentration [24]. In 2005 Reimers et al. showed that this reduction could probably be attributed to the estrogenic component [24].
Additionally in 2016 Reimers et al. showed that HRT users had significantly lower mean lamotrigine CDRs than their respective matched controls. Of the HRT users 85% used estradiol and 15% used estriol [13]. In another study a decline in lamotrigine levels was found in two subjects using HRT containing conjugated equine estrogens plus medroxyprogesterone [11].
While the SmPC of Lamictal® only describes a drug interaction between lamotrigine and ethinylestradiol/levonorgestrel, it does warn for a possible interaction with other oral contraceptives or HRT [1].
SHB monitors an interaction between lamotrigine and HRT in their medication monitoring system [18]. Stockley's Drug Interactions warns of an interaction between lamotrigine and HRT [19]. The KNMP doesn't monitor an interaction between lamotrigine and HRT but does monitor an interaction between lamotrigine and hormonal contraceptives containing estradiol [20].

The interaction between lamotrigine and estrogens is not described in the SmPC of estradiol/dydrogesteron (Femoston® or Femoston continu®) [3,4].

Both the report received by the Netherlands Pharmacovigilance Centre Lareb and the literature discussed above indicate that attention for a possible drug interaction between lamotrigine and estradiol/dydrogesteron is warranted. Also attention for this interaction is warranted for other products containing estradiol or products containing other estrogens.

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This signal has been raised on May 31, 2023. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl