Epilepsy & Behavior 22 (2011) 548–551

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Add-on lacosamide: A retrospective study on the relationship between serum concentration, dosage, and adverse events

Barbara Hillenbrand, Ilona Wisniewski, Uta Jürges, Bernhard J. Steinhoff *

Kork Epilepsy Centre, Kehl-Kork, Germany

ARTICLE INFO

Article history:
Received 11 July 2011
Revised 24 August 2011
Accepted 26 August 2011
Available online 1 October 2011

Keywords:
Lacosamide
Therapeutic range
Serum concentration
Weight-related dosage
Sodium channel blockers

ABSTRACT

We performed a retrospective study in patients with poorly controlled epilepsy treated with add-on lacosamide (LCM) to investigate the relationship of LCM-related adverse events with LCM serum concentration and weight-dependent dosage. We collected serum concentrations, weight-related dosages, and occurrences of the seven most frequent adverse events according to the randomized double-blind, placebo-controlled trials. Seventy of 131 patients could be sufficiently evaluated. LCM serum concentrations and weight-related dosages in patients with and without typical adverse events did not differ significantly. Closer analysis of the data suggested that dizziness as the leading adverse event occurred significantly more often if LCM was combined with classic sodium channel blockers. There was a significant correlation between LCM serum concentrations and co-medication, so there is still evidence for dependent variables that might have a relevant impact in individual cases. However, our data do not allow definition of a safety range for LCM.

1. Introduction

Lacosamide (LCM) was officially approved in Germany for add-on treatment of adults with partial-onset seizures in 2008. The efficacy and tolerability of LCM had been evaluated in three placebo-controlled randomized, double-blind studies in adults with difficult-to-treat partial-onset seizures. In these studies, LCM maintenance dosages were 200, 400, and 600 mg/day [1], 200 and 400 mg/day [2], and 400 and 600 mg/day, respectively [3]. A twice-daily dosing regimen was used in all studies. According to a pooled analysis of all three studies [4] the most frequent adverse event in these randomized trials was dizziness, which was reported by 16, 30, and 53% of patients at doses of 200, 400, and 600 mg/day, respectively, compared with 8% for placebo. Other adverse events that showed some relationship to dose include nausea and vomiting, abnormal coordination, tremor, visual disturbances, and fatigue. Somnolence was uncommon, even at high doses. The incidence of adverse events was markedly higher during titration than during maintenance, suggesting that a slower titration than in the clinical trials may be beneficial in some instances.

Lacosamide serum concentration may be measured by high-performance liquid chromatography coupled with mass spectroscopy (LC-MS) [5]. Therapeutic drug monitoring (TDM) and weight-related dosages may be useful for a rational therapeutic regimen and were used particularly with first- and second-line AEDs [6]. Although serum concentrations may be measured for most of the new AEDs [5], in most instances, the therapeutic relevance is less well defined although therapeutic ranges are given for almost every new AED in the literature [7]. The less reliable data on new AEDs result partly from a lack of reliable investigations about a potential therapeutic range and do not necessarily mean that TDM is not helpful [6]. Lamotrigine (LTG) and topiramate (TPM) are examples where TDM appears to be helpful either in reflecting changes during hormonal contraception or pregnancy for LTG [8–10] or in defining a safety range that should be intended to avoid adverse events of TPM [11].

As the leading side effects of LCM are typical neurotoxic effects such as dizziness, we thought that there might be a similar range for this new AED. We therefore used the methodology of Fröscher et al. [11] to investigate the relationship between serum concentration and adverse events in the case of LCM as add-on-therapy. A significant correlation would allow the specification of an approximate upper limit for a "therapeutic range" of LCM serum concentrations. Furthermore, we examined whether adverse events of LCM correlate with the weight-related dosage.

Recent literature indicated that add-on LCM might be better tolerated in combination with AEDs that do not act via the classic voltage- and use-dependent blockade of sodium channels [12,13]. Therefore we additionally addressed whether the mode of action of the concomitant AEDs influenced our findings.

2. Methods

We retrospectively assessed the data on 131 adolescent and adult inpatients and outpatients with poorly controlled epilepsy who

* Corresponding author at: Epilepsiezentrum Kork, Landstrasse 1, 77694 Kehl-Kork, Germany. Fax: +49 7851842555.
E-mail address: bsteinhoff@epilepsiezentrum.de (B.J. Steinhoff).

1525-5050/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2011.08.032

had been treated with LCM over an approximately 2-year period (between September 2008 and December 2010) at our Epilepsy Centre. Inclusion criteria were as follows: Uptitration was undertaken at 50- or 100-mg increments weekly, serum concentrations and dosages (mg/kg) of LCM and the concomitant anticonvulsants (AEDs) were assessed after a 6-month period (patients without adverse events) and at the time of an adverse event that had to be clearly documented and defined. For all patients without an adverse event, blood samples were taken 0.5 to 4 hours after the morning dose (many patients attending our outpatient clinic live quite a distance from the hospital); therefore, blood examinations could not be done before drug intake. For patients with an adverse event, blood samples were taken during the clinical manifestation of the side effect, which usually also occurred 0.5 to 4 hours after drug intake, but not necessarily exclusively in the morning. We listed the most frequent adverse events as dizziness, visual disturbance/diplopia, abnormal coordination, fatigue, nausea/vomiting, headache, and tremor. Age, gender, seizure types, compliance, and concomitant medications were also documented. In the case of combination therapy, serum concentrations and dosages of the following anticonvulsants were measured: LTG, levetiracetam (LEV), oxcarbazepine (OXC; in cases of OXC treatment we measured MHD, i.e., the monohydroxy derivative of OXC [14]), phenobarbital (PB), carbamazepine (CBZ), phenytoin (PHT), valproic acid (VPA), clobazam (CLB), zonisamide (ZNS), topiramate (TPM, pregabalin (PGB), sultiame (STM), rufinamide (RUF), and eslicarbazepine acetate (ESL) (as MHD is also the major metabolite of ESL, though in another composition of the enantiomers [15], we measured MHD concentrations in cases of ESL treatment).

Lacosamide serum concentrations were determined by LC-MS. Serum concentrations of LEV, ZNS, TPM, PGB, and CLB were also determined by LC-MS. MHD, LTG, STM, and RUF were determined by classic high-performance liquid chromatography with UV detection (HPLC). CBZ, VPA, PHT, and PB were determined by fluorescence polarization immunoassay (FPIA) [5].

The lack of homogenicity of the data in the other cases in this retrospective analysis (in the majority of these cases, blood samples were not taken at the time of the adverse event) allowed inclusion of only the findings for 70 patients. The demographic and clinical characteristics of the patients are given in Table 1.

Thirty-seven patients were treated with LCM in combination with one additional anticonvulsant, 24 patients in combination with two anticonvulsants, and 10 patients in combination with three additional anticonvulsants (Table 2).

2.1. Statistical analysis

Statistical methods included descriptive statistics for specification of the total sample, and the Mann–Whitney *U* test for differences between patients without those with adverse events relating to LCM serum concentrations and LCM dosages.

Table 1
Demographic and clinical characteristics of patients ($n = 70$).

Age, years	
Median	37.4
Range	17–68
Gender (M/F)	33/37
Focal seizures	
Without impairment of consciousness	58
With impairment of consciousness	66
Evolving into bilateral convulsive seizure	68
Compliance during the study ($n = 70$ patients)[a]	
Yes	66 (94.3%)
No	0 (0%)
Uncertain	4 (5.7%)
Mean number (range) of AEDs taken before beginning LCM therapy	9.4 (4–19)

[a] Retrograde interview about the reliability of the intake of medication.

Table 2
Concomitant antiepileptic drugs at the time of the adverse event or 6 months ($n = 70$ patients).

	n	Dose (mg)	Serum concentration (μg/mL)
Lamotrigine	22	455 (250–800)[a]	8.2 (3.1–18.2)
Levetiracetam	19	2645 (750–4000)	22.9 (1.8–62.3)
Oxcarbazepine	17	2100 (600–4800)	26.8 (7.2–42.2)
Phenobarbital	12	169 (50–400)	31.1 (12.9–44.3)
Carbamazepine	10	1790 (1200–2700)	11.9 (8.6–16.0)
Phenytoin	7	311 (225–400)	18.1 (7.6–30.5)
Valproic acid	7	1957 (1000–2900)	75.0 (62.6–96.1)
Clobazam	7	21.4 (15–30)	Not determined in all cases
Zonisamide	5	380 (200–500)	18.5 (12.5–18.6)
Topiramate	4	338 (150–600)	7.7 (3.3–14.9)
Pregabalin	2	400 (300–500)	5.0 (2.0–7.9)
Sultiame	1	400	8.5
Rufinamide	1	2000	11.4
Eslicarbazepine acetate	1	2000	32.6

[a] Median (range).

To examine the influence of the co-medication on the occurrence of adverse events, we performed three independent multivariate linear regressions using the binomial variable dizziness as the dependent variable and total number of anticonvulsants, number of sodium blockers, and number of other types of drugs as categorical predictors. Three logistic linear regression models were also made, again using "dizziness" as the binomial dependent variable, with total number of anticonvulsants (model 1), number of sodium blockers (CBZ, OXC, ESL, PHT, and LTG) (model 2), and number of other types of drugs (model 3) as categorical predictors, and serum concentrations and dosages of LEV, PB, VPA, CLB, ZNS, TPM, PGB, STM, and RUF as continuous variables.

3. Results

Thirty-two of 70 patients (46%) experienced one or more adverse events (Table 3). The LCM serum concentration and the LCM weight-related dosage at the time of these adverse events were compared with the corresponding values of patients who had experienced no adverse event over a 6-month period. LCM serum concentrations and LCM weight-dependent dosages (mg/kg) did not differ significantly between patients without an adverse event and patients with typical clinical adverse events (Table 4).

As described above we performed three independent multivariate linear regressions to examine the influence of the co-medication on the occurrence of adverse events. Intake of classic sodium blockers was associated with a significant *P* value (0.03) for the occurrence of "dizziness" (Table 5).

Each model—"anticonvulsant medications excluding sodium channel blockers," "sodium channel blockers only," and "all anticonvulsants"—was compared with the dosage (mg/kg) and serum concentration of LCM. In all subgroups, *P* values were significant for serum concentration

Table 3
Adverse events in patients treated with lacosamide.

Adverse event	*n*	% of 70 patients
Dizziness	17	24
Visual disturbance/diplopia	14	20
Abnormal coordination	5	7
Fatigue	4	6
Nausea/vomiting	4	6
Headache	4	6
Tremor	1	1