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Fluctuation of lacosamide serum concentrations during the day and occurrence of adverse drug reactions — First clinical experience

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Summary
Purpose: To obtain better understanding of the effect of lacosamide (LCM) in clinical practice, laboratory and clinical data of 17 patients under treatment with LCM as an add-on antiepileptic drug (AED) were retrospectively evaluated.
Methods: Total LCM serum concentrations were obtained at hourly intervals for up to 5 h and 8 h after morning dose. Adverse drug reactions (ADR) were assessed.
Results: LCM serum concentrations showed high fluctuations during the day with a steep increase within the first 3 h after intake (mean 87.8%; range: 44.4—149.0%) under b.i.d. Mean trough and peak concentrations of LCM were 5.0 μg/ml (range: 1.8—9.5 μg/ml) and 9.7 μg/ml (range: 4.0—18.3 μg/ml), respectively; mean dose 353 mg/d (range: 200—600 mg/d). Twelve patients showed ADRs. After conversion to t.i.d. or dose reduction LCM serum concentration showed lower fluctuations during the day and a lower increase after intake (mean: 50.0%, range: 27.1—66.7%); peak LCM was 9.4 μg/ml (range: 4.7—11.6 μg/ml), mean dose 388 mg/d (range: 300—500 mg/d). These interventions led to amelioration of the ADR.
Conclusion: Changing the dose regimen from two to three times daily could reduce fluctuations of LCM during the day and improve tolerability of LCM in patients with ADR.

Introduction

Lacosamide (LCM) is a novel antiepileptic drug currently licensed in the EU for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged sixteen years and older (European Medicines Agency, 2008a,b). After oral adminis-

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Table 1 Demographic characteristics of patients, LCM dosage and co-medication.

Patient	Age	Gender	Weight [kg]	Dose LCM [mg]	Co-medication [mg]		
1	28	Male	104	200 (100—0—100)	LTG (700)		
2a	47	Male	89	250 (150—0—100)	OCBZ (2100)	PB (200)	
2b				300 (100—100—100)	OCBZ (1800)	PB (200)	
3a	49	Male	58	600 (300—0—300)	LTG (400)		
3b				500 (100—150—250)	LTG (450)		
4a	53	Female	70	400 (200—0—200)	LTG (100)		
4b				350 (150—50—150)	LTG (100)		
5	22	Male	69	350 (150—0—200)	LTG (200)		
6a	43	Male	69	500 (250—0—250)	LTG (150)		
6b				400 (150—100—150)	OCBZ (1800)		
7	52	Male	75	400 (200—0—200)	LEV (3000)		
8	37	Female	82	400 (200—0—200)	LEV (4000)		
10	49	Female	74	400 (200—0—200)	OCBZ (1650)	PB (125)	
11	27	Female	127	400 (200—0—200)	LEV (4000)	VPA (300)	LTG (400)
12	54	Male	70	300 (150—0—150)	CBZ (1050)	ZNS (50)	BROM (1700)
13	44	Female	56	500 (250—0—250)	OCBZ (1950)		
14	55	Female	54	200 (100—0—100)	OCBZ (1800)		
15	27	Male	72	250 (100—0—150)	OCBZ (2400)		
16	40	Male	86	200 (100—0—100)	OCBZ (1200)	VPA (900)	
17	47	Male	82	300 (150—0—150)	OCBZ (1200)	PRM (500)	

tration it is completely and rapidly absorbed with negligible first-pass-effect (Thomas et al., 2007). Ninety-five percent of the drug is renally eliminated and elimination half-life is about 13 h in patients with normal renal function. Maximum serum concentration (C_{max}) is reached after 1—4 h; C_{max} is dose dependent and plasma concentration shows a proportional relationship in the dose ranges of 100—800 mg/day (Horstmann et al., 2002). Studies suggest that LCM is generally well tolerated with just mild or moderate side effects. The most common treatment-emergent adverse events, reported in >10% of patients, were dizziness, headache, nausea and diplopia (European Medicines Agency, 2008b).

However, only a few pharmacokinetic data have been published concerning fluctuations of LCM serum concentrations during the day and their possible impact on the tolerability of the drug (Ben-Menachem et al., 2007; Halász et al., 2009; Cawello et al., 2010) (for further details see Discussion).

Therefore, we retrospectively examined the data of 17 patients with daily doses of LCM between 200 and 600 mg/d as an add-on AED in whom LCM serum concentrations during the day and adverse drug effects were assessed.

Methods

Patients

We conducted a retrospective analysis of LCM serum concentration profiles determined as part of clinical routine. The examinations were done while the patients were under in-patient care of the Bethel Epilepsy Centre, Bielefeld, Germany, a tertiary reference centre for epilepsy. Reasons for assessing the serum concentration profile were either suspected drug side effects or the suspicion that the individual tolerance level might be reached with further up-titration. In this latter case the examinations were done in order to estimate the chance for further up-titration. The demographical data of the patients are summarized in Table 1.

Blood sampling

Total serum concentrations of LCM were assessed as trough levels (08.00 h) and then at 09.00 h, 10.00 h, 11.00 h, 12.00 h, 13.00 h, and 16.00 h. In some cases LCM serum concentrations were additionally determined at 18.00 h ($n = 1$), 20.00 h ($n = 5$), 21.00 h ($n = 2$) or 22.00 h ($n = 1$).

In four patients the serum concentration profiles were checked again after change from b.i.d. to t.i.d. The daily profiles of LCM were assessed at steady-state (last change of LCM dose > 3 days).

Assessment of ADRs

ADRs were assessed by patients' self-reports and by clinical examination. If possible, the patients were asked to answer a validated self-rating questionnaire for the assessment of adverse drug events (FENAT) (May et al., 2009), and assessments of body sway (posturographic examinations) (Noachtar et al., 1998; Specht et al., 1997) were done at the times of blood drawing (±15 min).

Determination of serum concentrations of LCM and of concomitant AEDs

We used liquid chromatography with a mass specific detector (1100 LC-MSD, Agilent Technologies, Germany) for the quantitative determination of LCM. The serum samples were prepared by liquid—liquid extraction with acetonitrile—methanol (9:1) containing the internal standards cyproheptadin and 10,11-dihydro-carbamazepine. Both substances from Aldrich (Germany); LCM was supplied by UCB S.A. (Belgium). LCM and the internal standards were separated on a ZORBAX Eclipse 5-Micron column from Agilent Technologies (Germany) at 45 °C with a gradient of water (A) and methanol (B) and a flow rate of 0.5 ml/min. Detection was achieved using an Agilent 6110 single quadrupole mass detector. The day-to-day coefficient of variation

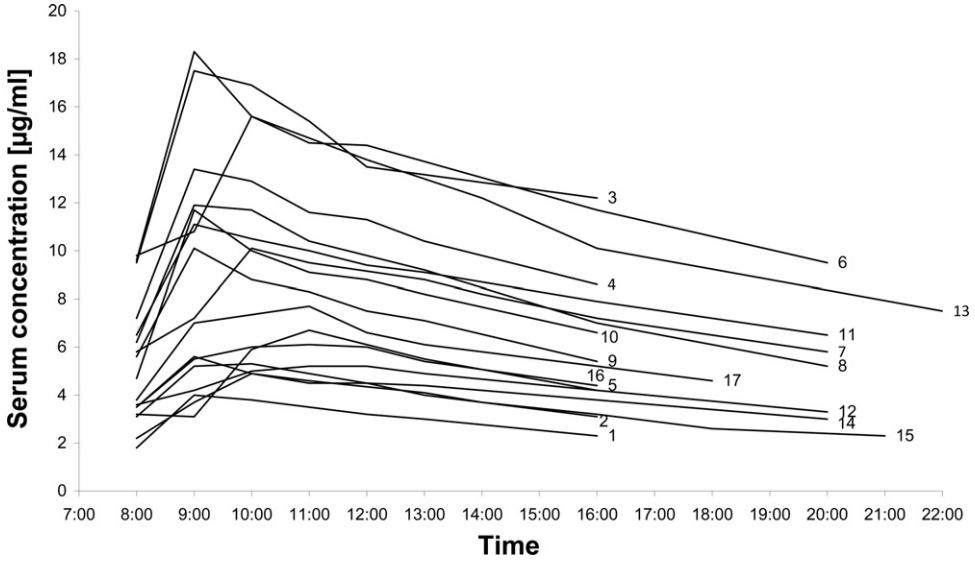

Figure 1 Serum concentration profiles of 17 patients on LCM b.i.d.

(CV) in a pooled serum, the remaining serum being frozen again over night, was below 3% for the LCM concentrations. The limit of detection was found to be at 0.1 μg/ml and the limit of quantitation was defined at 0.2 μg/ml serum sample.

Statistical evaluations

The results were analysed by means of descriptive statistical methods.

The swing ($100\cdot(C_{max} - C_{min})/C_{min}$) and in addition the percent increase of LCM serum concentration after intake of the morning dose ($100\cdot(C_{max} - C_{morning\ (8\,h)})/C_{morning\ (8\,h)}$) were calculated as measures of the daily fluctuations of LCM.

The elimination half-life of LCM was estimated using the program TOPFIT 2.0 (R) (Heinzel et al., 1993). For statistical calculations, SPSS for Windows 18.0 was used.

Results

Twenty-one profiles of total serum concentrations of LCM from 17 patients with epilepsy were determined. The demographical data of the patients, the LCM dosage and concomitant AEDs at the days of the assessment of serum profiles are summarized in Table 1.

Medication

LCM was used as an adjunctive AED in patients with focal epilepsy. The maximum recommended dose of 400 mg/day was exceeded in 3 cases for clinical reasons. The aim was to obtain the best possible antiepileptic effect. Dose escalation was initially done in steps of 100 mg per week as recommended by the manufacturer. This was changed to 50 mg every five days after occurrence of adverse effects that were supposed to be a consequence of this rather fast way of uptitration. Dose adjustments of concomitant AEDs have been conducted if necessary.

LCM doses were given b.i.d. in the morning (at 08.00 h) and in the evening at 18.00 h ($n = 2$) or 20.00 h ($n = 15$); in t.i.d. regimes an additional dose was given 6 h after the morning dose in 3 patients and 7 h after the morning dose in one patient. The evening dose was given at 20.00 h ($n = 2$) and 22.00 h ($n = 2$), respectively. At the time of assessment LCM was given in addition to 1.6 concomitant AEDs (range 1—3) (Table 1).

Fluctuations of LCM serum concentrations during the day

The daily profiles were assessed under a mean LCM dose of 353 mg/d (200—600 mg/d). The daily fluctuations of LCM serum concentration of the 17 patients on a b.i.d. dosage regimen are shown in Fig. 1. Fig. 2 displays the fluctuations using normalised morning values (= 100). The maximum LCM concentrations during the day were about 87.8% higher than the morning concentrations before drug intake (range: 44.4—149.0%). Under LCM b.i.d nine patients showed their measured peak concentration 1 h after intake, four patients 2 and four patients 3 h after intake.

In four patients a second daily profile has been measured (see Fig. 3 for the corresponding serum concentration profiles) after conversion to a t.i.d. dose regimen. LCM serum concentrations showed lower fluctuations during the day and a lower increase of LCM during the first hours after intake (mean 50.0%; range: 27.1—66.7%). See Tables 2 and 3 for the fluctuations of LCM serum concentration in detail.

ADRs during LCM therapy

Twelve patients showed 36 ADRs: dizziness ($n = 9$), nystagmus ($n = 5$), increased body sway (5), ataxia ($n = 3$), nausea ($n = 3$), diplopia ($n = 3$), fatigue ($n = 3$), vomiting ($n = 2$), tremor ($n = 2$) and headache ($n = 1$). The total number of ADRs exceeds the number of patients as some patients had more than one ADR. Self-reported complaints were counted as ADRs if confirmed by clinical examination at the time of onset ($n = 11$) and by additional posturographic examinations ($n = 5$) at the time of blood drawing (±15 min) or if dizzi-

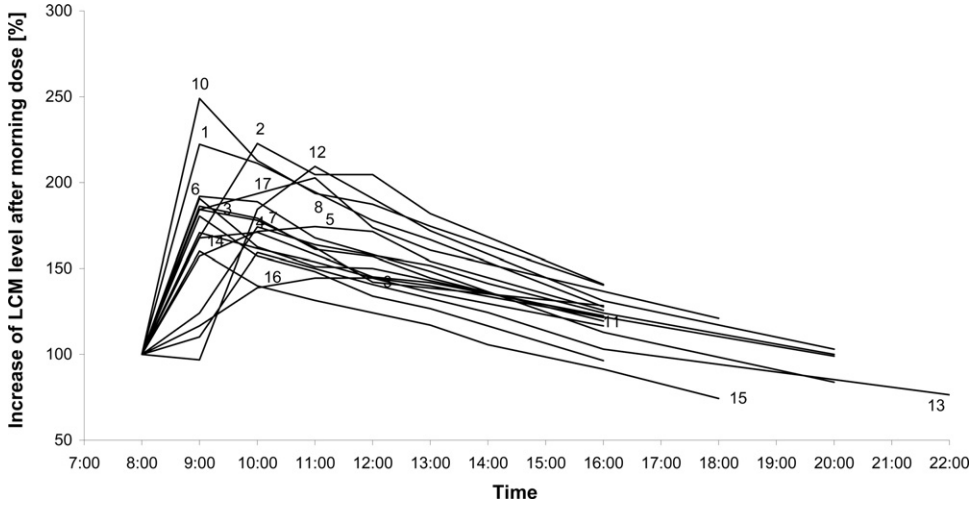

Figure 2 Percentage increase of LCM serum concentrations after intake of the morning dose in 17 patients on LCM b.i.d.

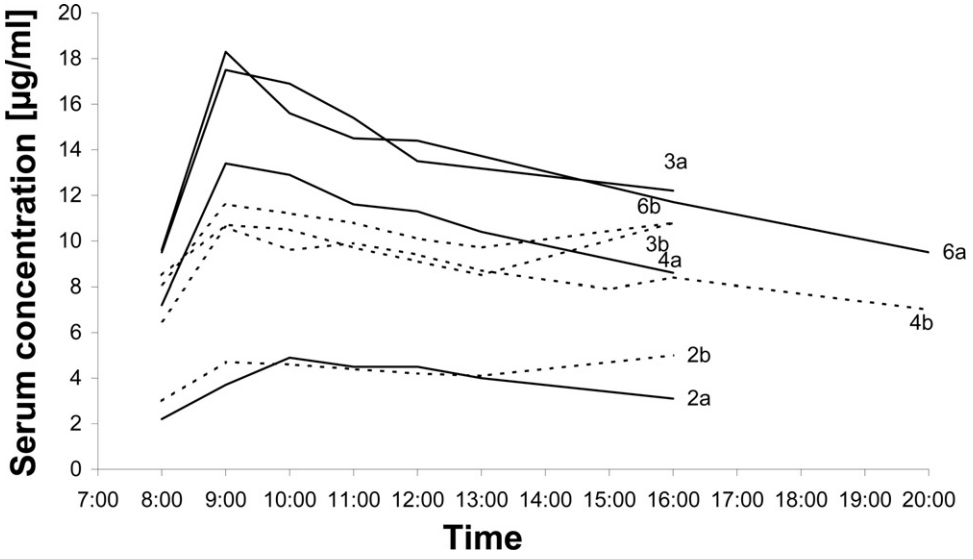

Figure 3 Serum concentration profiles of 4 patients on LCM b.i.d. and after conversion to LCM t.i.d.

ness as a complaint persisted over more than 3 days ($n = 1$). Eight patients additionally answered the self-rating questionnaire for the assessment of adverse drug events (FENAT) (May et al., 2009).

In some cases the onset of ADRs seemed to be in close temporal relationship to the measured peak serum concentrations of LCM. Examples are shown in Supplementary Figs. 1 and 2.

Table 2 Fluctuations of LCM levels during the day in 17 patients on LCM b.i.d.

	Mean	SD	Min	Max
LCM dose (mg/day)	353	117	200	600
LCM morning level (µg/ml)	5.3	2.6	1.8	9.8
LCM max. after intake of LCM morning dose (µg/ml)[a]	9.7	4.6	4.0	18.3
t_{max} (h)	1.6	0.8	1.0	3.0
Increase of LCM levels after intake of the LCM morning dose (%)	87.8	26.6	44.4	149.0
LCM min. during the day (µg/ml)	5.0	2.4	1.8	9.5
LCM max. during the day (µg/ml)	9.7	4.6	4.0	18.3
Swing of LCM levels during the day (%)	99.3	27.9	48.6	148.9
Estimated elimination half-life (h)	10.7	2.0	7.5	14.6

[a] LCM maximum level measured after morning dose and before evening dose

Table 3 Fluctuations of LCM levels during the day in 4 patients on LCM b.i.d. and after conversion to LCM t.i.d.

		Mean	SD	Min	Max
LCM dose (mg/day)	b.i.d.	438	149	250	600
	t.i.d.	388	85	300	500
LCM morning level (μg/ml)	b.i.d.	7.1	3.5	2.2	9.6
	t.i.d.	6.5	2.5	3.0	8.5
LCM max. after intake of LCM morning dose (μg/ml)	b.i.d.[a]	13.5	6.1	4.9	18.3
	t.i.d.[b]	9.4	3.2	4.7	11.6
t_{max} (h)	b.i.d.	1.3	0.5	1.0	2.0
	t.i.d.	1.0	0.0	1.0	1.0
Increase of LCM levels after intake of the LCM morning dose (%)	b.i.d.	95.9	18.1	84.2	122.7
	t.i.d.	47.2	16.5	25.9	63.1
LCM min. during the day (μg/ml)	b.i.d.	7.1	3.4	2.2	9.5
	t.i.d.	6.5	2.5	3.0	8.5
LCM max. during the day (μg/ml)	b.i.d.	13.5	6.1	4.9	18.3
	t.i.d.	9.5	3.0	5.0	11.6
Swing of LCM levels during the day (%)	b.i.d.	96.4	17.9	84.2	122.7
	t.i.d.	50.0	18.5	27.1	66.7
Estimated elimination half-life (h)	b.i.d.	11.7	1.2	10.1	12.7
	t.i.d.	12.5	0.7	11.6	13.3

[a] LCM maximum level measured after morning dose and before evening dose.
[b] LCM maximum level measured after morning dose and before afternoon and evening dose, respectively.

Switch of drug regimen from b.i.d. to t.i.d. — Report of individual cases

In four patients with ADR the dose regimen of LCM was changed from two to three times daily in order to decrease LCM serum fluctuations and thus to improve tolerability. In all patients the swing of LCM serum concentration during the day as well as the percent increase of LCM serum concentration after intake of the morning dose has been reduced. In two of the four cases, in patient No. 3 (ADRs: dizziness, ataxia, nausea, fatigue) and No. 4 (ADRs: diplopia, tremor) this intervention, accompanied by dose adjustment of LCM, led to complete remission of the ADR. In patient No. 2, ADRs (b.i.d.: dizziness, nystagmus, ataxia, nausea, fatigue; t.i.d.: dizziness, nystagmus, nausea) were allayed by switching to t.i.d. and simultaneous decrease of OCBZ (300 mg) but increase of LCM (50 mg).

The course of patient No. 6 was more complex: He had no ADR at discharge under LCM 250 mg b.i.d. in combination with LTG 150 mg. A few months later he was admitted to our centre because of ADRs (dizziness, nystagmus, nausea, fatigue) on LCM 400 mg t.i.d. and oxcarbazepine (OXC) 1800 mg substituted for LTG.

Discussion

Our study has several limitations: First, the sample size is small and there was no fixed schedule — neither for up-titration or target doses of LCM nor for concomitant medication. This is due to the fact that the data were obtained as part of clinical routine. Furthermore, all patients were on combination therapy. Therefore, an influence of the co-medication on the occurrence of ADRs has to be considered.

Despite these limitations, our results indicate that LCM showed marked fluctuations of serum concentrations during the day, especially a rapid increase within the first hours after intake.

Only a few data have been published concerning pharmacokinetic parameters of LCM. In a study of Ben-Menachem et al. (2007) *m*ean LCM plasma concentration (2—4 h after trial medication dosing) at the end of a 12-week maintenance period for a 400 mg/day dose group has been reported at 9.35 μg/ml ($n = 83$).

Halász (Halász et al., 2009) reported a mean LCM plasma concentration at 7.4 μg/ml ($n = 159$) under the same conditions. A study of Cawello et al. (2010), investigating the pharmacokinetic interaction between lacosamide and carbamazepine (CBZ), was designed to permit an intra-subject comparison of the primary parameters $C_{max,ss}$ and $AUC_{\tau,ss}$ and the secondary measures $t_{max,ss}$ and C_{trough} in male healthy volunteers. These volunteers got LCM 200 mg b.i.d., which is similar to the mean dose of 353 mg per day in our investigation. $C_{max,ss}$ is reported at 9.1 ± 1.6 μg/ml (LCM alone) and at 9.9 ± 2.0 μg/ml (LCM + CBZ), which is also comparable to our findings (9.7 μg/ml). Fluctuations of LCM during the day were not quantified in that study. However, from their Fig. 2 (see Cawello et al., 2010) showing the time course of LCM serum concentrations a mean increase of approximately 70% of LCM serum concentrations after intake can be estimated.

The mean percent increase of LCM serum concentration after intake of the morning dose in our patients is about 18% higher than in the Cawello study (Cawello et al., 2010). More differences appear in data of t_{max} and $t_{1/2}$. In our investigation maximum plasma concentration is reached between 1 and 3 h (mean 1.6 h) compared to 2.4 ± 1.0 h (LCM alone) and 2.2 ± 0.9 h (LCM + CBZ) (Cawello et al., 2010). Also the estimated elimination half-life is somewhat shorter than reported by Cawello et al. (2010) (10.7 h vs. 12.8 h). These differences are in accordance with the higher fluctuations of LCM serum concentration in our investigation.

It should be noted that the fluctuations of LCM in our patients under enzyme-inducing medication (PB, OCBZ, CBZ or PRM, $n = 9$) were not significantly different ($p > 0.1$; two-sided Mann—Whitney test) from that patients without ($n = 8$). This is in agreement with other studies (Ben-Menachem et al., 2007).

It will not be feasible in most in- or out-patient settings to collect blood samples at multiple times during the day, but assessment of serum concentrations of LCM as trough levels compared to a sample taken at the time of occurrence of ADR might be helpful in specific situations. Determination of serum concentrations is indicated in case of ADR in many AEDs (Brandt et al., 2008). This could to be true for LCM also.

Conclusion

Despite the above mentioned limitations (e.g. limited number of patients, only partially standardized protocol), the following conclusions can be drawn: LCM serum concentrations show high fluctuations during the day with a steep increase and the maximum within the first 3 h — in many patients already within the first hour — after intake. This finding could be expected as it is known from other AEDs with similar half-life values, but has — to our knowledge — not been reported for LCM before.

LCM serum concentrations are subject to wide individual differences, but adjunctive concomitant antiepileptic drugs appear to have no effect on LCM pharmacokinetics.

In case of ADRs, conversion to t.i.d. LCM could be a promising alternative to dose reduction or discontinuation. This strategy is in use in other AEDs with similar half-life as well, but has also — to our best knowledge — not been reported for LCM so far.

Even though LCM is described with minimal dosing and monitoring requirements (Halford and Lapointe, 2009), determining a serum concentration profile of LCM in case of ADR can be useful.

Confirmation of our data by a larger prospective study under standardized conditions would be desirable.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eplepsyres.2011.03.019.

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