Successful treatment with adjunctive lacosamide in a patient with long term “drug resistant” focal epilepsy

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SUMMARY

Introduction. A significant number of patients suffering from epilepsy prove to be resistant to antiepileptic drugs (AEDs). Recent studies, however, suggest that 10–20% of seemingly drug resistant patients may still become seizure-free under the influence of subsequent dosage modifications.

Case report. We report on a young man with cryptogenic focal epilepsy. He had his first seizure at the age of fifteen. His seizure frequency was decreased during the following 11 years. However, seizure-freedom was never achieved even though he was treated with twelve to fourteen different AEDs during this time. Intensive presurgical evaluations did not allow identification of a surgically remediable focus. Adjunctive treatment with lacosamide 400 mg/day was not successful. However, the patient became seizure-free immediately after an increase of the lacosamide dose up to 500 mg/day. The patient is now seizure-free for more than two years based on a combination of 500 mg lacosamide and 350 mg lamotrigine, followed by 550 mg and 250 mg, respectively.

Discussion and conclusion. This case report highlights that there is always a chance that modifying the medication can result in a drug-resistant epilepsy patient experiencing a significant reduction of seizures and becoming seizure-free. The decisive step in this example was the off-label prescription of a high dose of lacosamide which the patient tolerated well.

Key words: epilepsy • drug resistance • lacosamide

INTRODUCTION

The majority of individuals who develop epilepsy achieve remission; 8–40%, however, develop drug resistant epilepsy (Fröscher, 2012). According to the definition of the International League Against Epilepsy (ILAE) “drug resistant epilepsy” is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010). In the prospective study of Schiller and Najjar (2008) the percent of patients rendered seizure-free by the newly administered AED treatment dropped to 16.6% after failure of two to five previously tried AEDs, and 0% after failure of six or seven previously tried AEDs.

A substantial number of drug resistant patients benefit from non-pharmacological treatment modalities, especially epilepsy surgery (Fröscher, 2012). If surgery is not an option in drug resistant patients with epilepsy, changes in medical regimens should be always considered.

The classification of a patient’s epilepsy as drug resistant at a given time is valid only at the time of assessment.
ment and does not necessarily imply that the patient will never become seizure-free on further adjustment of AED therapy (Kwan et al., 2010). Recent studies appear to suggest that 10–20% of seemingly drug resistant patients may still become seizure-free with subsequent drug optimization (Callaghan et al., 2007; Luciano and Shorvon, 2007; Munger Clary and Choi, 2011; Fröschler and Rösche, 2013). The following case report highlights that there is always the possibility that a patient with drug resistant epilepsy can experience a significant seizure reduction and become seizure-free upon a change in medical regimen.

The patient gave his informed consent to publish his data.

CASE REPORT

The male patient M was born in 1985. His childhood development and the family history were uneventful.

At age 15, M had measles with high temperature; measles encephalitis was not suspected. Three months later the patient had his first unclear attack when playing tennis: he had a feeling of weakness and fell to the ground. After a further three months M had his first generalized tonic-clonic seizure (GTC) when he was watching television. M was sent to a hospital where he had his second GTC some hours later. Phenytoin (PHT) was prescribed and it is probable that the PHT dose was low since the highest known serum concentration was only 4.2 mg/L. In the following period M experienced at first one “absence seizure” (probably complex focal seizures (CFS)) per week and GTCs, predominantly during sleep. The exact frequency of seizures was not documented; the seizures tended to cluster. Initial symptoms of the seizures during wakefulness were a feeling of unsafety and of gastric discomfort (“auras”). Precipitating mechanisms were physical stress, fright, acute pain, fever, and sleep deprivation.

The patient was repeatedly hospitalized in epilepsy centres and his seizures were documented by video-electroencephalography. The concluding diagnosis was "cryptogenic focal epilepsy with simple focal (SFS), complex focal and secondary generalized tonic-clonic seizures". The initial PHT-monotherapy was soon replaced by valproic acid (VPA); probably because PHT in the administered dosage was not effective. Thereafter, numerous AED schedules followed, both, as monotherapy or in combination. After PHT and VPA, the following substances were administered (in approximate chronological sequence): Oxcarbazepine, carbamazepine (probably administered), phenobarbital (probably administered), levetiracetam, lamotrigine (LTG), clonazepam (CZP), lorazepam, zonisamide, topiramate, pregabalin (PGB), sulthiame (STM) and finally lacosamide (LCM).

In 2007, M had 3 GTCs per month, in 2008 it were still 3–4 GTCs per year; CFS formed clusters every few weeks. The additional SFS had a frequency of 5–20 per month at this time. Occasionally the CFS passed into a nonconvulsive status epilepticus.

Two years after the onset of focal seizures M had been considered for surgical treatment. During the following years presurgical evaluation with intensive neuroimaging, video-EEG monitoring etc. was undertaken at 3 or 4 centres for epilepsy. Physical and neurological examination and imaging findings (head CT, MR) were always normal. Neurophysiologic examination and EEG findings did not allow identification of a surgically removable epileptic focus. At the beginning of 2009, M experienced a series of CFS and/or GTCs and he had a cluster of seizures every 6–8 weeks. This unfavourable situation entailed a transient combination therapy with five AEDs: LCM was added to the combination of LTG, PGB, STM and CZP. The initial dosage of LCM was 50 mg b.i.d.; STM and CZP were slowly withdrawn. In mid2011, M was treated with a combination of LCM 400 mg per day, LTG 300 mg per day, PGB 750 mg per day, and CZP 0.3 mg per day. With this drug combination M had one cluster of CFS per month typically lasting 3–4 days. In comparison to the situation before the treatment with LCM, seizure frequency was essentially unaffected.

M contacted us for the first time in September 2011. At that time M was treated per day with LCM 400 mg (200 mg b.i.d.), LTG 350 mg, PGB 300 mg and a small dose of CZP (< 0.3 mg). We increased the dosage of LCM up to 500 mg per day (200–300 mg) and withdrew PGB and CZP. Transiently this change induced irritability and tiredness (this could have been the effect of the increase of the LCM dosage or of the withdrawal of PGB and/or CZP). With the combination of LCM (500 mg per day and later 550 mg) and LTG (350 mg and later 250 mg) M became quickly seizure free and has remained seizure free since the beginning of October 2011 although in January 2014 it cannot be excluded that the patient had two “auras”: When playing volleyball he had two times a short feeling of insecurity. The LTG dose was reduced to 250 mg per day on the basis that the patient experienced a feeling of im-
balance approximately 15 minutes after the intake of LCM and LTG. Consequently, this probable adverse event disappeared.

In May 2013 the serum concentration of LCM was 5.5 mg/L and was relatively low in comparison to previous values at the same dosage (Tab. 1). With respect to the long lasting drug resistance in this patient, the dosage of LCM was prophylactically increased; this increase was tolerated well. LCM serum concentrations were determined by liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS), LTG serum concentrations were determined by on-line column-switching high-performance liquid chromatography with ultraviolet detection (HPLC with UV detection. Labor Dr. Gärtner, Ravensburg, Germany).

Electrocardiographic recordings were performed before the administration of LCM in 2009 and during the treatment with LCM 500 mg per day. The findings were normal and with no prolongation of the PR interval (Hoy, 2013; Wittstock et al., 2011). The inter-ictal routine EEG (rest wakefulness recording) when taking 500 mg and 550 mg LCM, respectively, showed a slow alpha rhythm (8.5–9/s), similar to that observed before the treatment with LCM, without any paroxysmal or focal activities. Clinical laboratory tests were normal; except in January 2014 a moderate increase of Gamma-Glutamyltransferase (GGT) was recorded, the value was 105 U/l (reference range: < 60 U/l).

M is able to practice his academic profession and is planning to get a driving licence; he also is able to practice sports and he is very happy on the success of the treatment.

### DISCUSSION AND CONCLUSION

In this case of “cryptogenic” focal epilepsy, drug resistance was present from the time of seizure onset in 2000 until 2011. The effective drug was LCM; this drug was approximately the 15th AED which had been prescribed to this patient. The decisive step was an increase of the LCM dosage beyond the maximum recommended daily dosage of 400 mg/day (Hoy 2013; Vimpat® product information 2013).

This case firstly underlines the significance of checking the appropriate dosage of a drug before one changes the drug, and secondly, that the ILAE definition of a “drug resistant epilepsy” (Kwan et al., 2010) and the negative results of Schiller and Najjar (2008; failure of six AEDs means “absolute” drug resistance) should not prevent perseverance to decrease seizure frequency of a seemingly drug resistant patients. As demonstrated in a series of studies, there is evidence that up to 10–20% of these patients enter remission after several years of continuous seizure activity and after trials of more than two drugs (Fröscher et al., 1989; Nelligan et al., 2011; Fröscher and Rösche, 2013). The reasons for this late response to AED treatment are yet to be identified.

The therapeutic efficacy of oral LCM as an adjunctive to other AEDs was evaluated in adults and in adolescents with focal-onset seizures in placebo-controlled studies and in clinical practice (Chung et al., 2010a; Hoy, 2013; Nelligan et al., 2011; Fröscher and Rösche, 2013). The reasons for this late response to AED treatment are yet to be identified.

### Table 1. Dosage and serum concentration of LCM and LTG at different time points.

| Date         | LCM dosage (mg) | LCM serum concentration (mg/L) | LTG dosage (mg) | LTG serum concentration (mg/L) | Interval¹ hours |
|--------------|-----------------|--------------------------------|-----------------|--------------------------------|-----------------|
| 2011 09 20   | 400             | 8.8                            | 350             | 6.1                            | n.a.³           |
| 2012 02 12   | 500             | 10.0                           | 350             | 5.6                            | n.a.            |
| 2012 05 02   | 500             | 7.3                            | 300             | 3.4                            | n.a.            |
| 2012 09 05   | 500             | 14.0                           | 300             | 6.1                            | n.a.            |
| 2013 01 09   | 500             | 11.0                           | 250             | 3.8                            | 3.5             |
| 2013 05 08   | 500             | 7.8                            | 250             | 4.3                            | 3.5             |
| 2013 05 23   | 500             | 5.3²                          | 250             | 3.7²                          | 1.0             |
| 2013 07 15   | 550             | 12.0²                          | 250             | 4.2²                          | 1.5             |
| 2013 09 04   | 550             | 11.0                           | 250             | 4.4                            | 4.5             |
| 2014 01 08   | 550             | 7.6                            | 250             | 3.1                            | 5.5             |

¹ Time interval between last drug intake and collection of blood sample (hours).
² Determined in a foreign laboratory.
³ Not available.
In the study of Chung et al. (2010b) patients randomized to LCM showed large reduction in secondarily GTCs, with median percent reductions in seizure frequency of 59.4% for LCM 400 mg/day and 93% for LCM 600 mg/day compared to 14.3% for placebo. LCM is approved for the adjunctive treatment of focal (partial-onset) seizures with and without generalization in adults and adolescents (aged 16–18 years) by the European Medicines Agency (EMEA) and in patients aged ≥17 years by the U.S. Food and Drug Administration (FDA) (Hoy, 2013). In both the European Union and the United States, LCM is approved only at doses up to 400 mg/day. A dosage of 600 mg/day, however, is not infrequently used in routine clinical practice (Chung, 2010; Zaccara et al., 2013), and also in the treatment of status epilepticus with intravenous lacosamide (Mula et al., 2012). The incidence of several treatment-emergent adverse events (dizziness, nausea etc.) was lower in the LCM 400 mg/day group than in the 600 mg/day group (Chung et al., 2010 b). The higher degree of toxicity in the LCM 600 mg/day groups seems to justify the decision of EMEA and FDA to exclude 600 mg/day from the approved dose range for drug-resistant partial-onset seizures (Zaccara et al., 2013). In the case of M, the approved dose of 400 mg/day was exceeded. With respect to the lasting drug resistance, we assessed this off-label-use as warranted. During 5 years of LCM treatment the patient had no unequivocal LCM related adverse events; the increase of the dosage from 500 mg to 550 mg was also well tolerated.

The cause of the elevated GGT value is unknown. The causal relationship with LCM is not probable. In the study of Chung et al (2010a) on LCM as adjunctive therapy for partial-onset seizures, results of clinical laboratory tests across treatment groups (200 mg/day, 400 mg/day, 600 mg/day) “did not identify any changes that appeared to be associated with LCM. Two patients had asymptomatic increases in ALT values”. With regards to M, the GGT increase could be associated to a temporary increase of alcohol intake.

The distinct fluctuations of the patient’s LCM serum concentration with the b.i.d. regimen are not unusual. In the study of Sattler et al. (2011) LCM serum concentrations showed high fluctuations during the day with a steep increase within the first three hours after drug ingestion. Mean trough and peak concentrations of LCM were 5.0 mg/L and 9.7 mg/L respectively (mean dose 353 mg/day [range: 200–600 mg/day]). Furthermore, the intervals between last drug intake and blood sampling could not be kept constant in the outpatient M, who lived far from the hospital. An effect on the LCM serum concentration by LTG is not expected (Conti et al., 2013; Patsalos, 2013). The fluctuations in LCM serum concentrations which we observed in this patient were within the reference range of 2.5–14 mg/L reported by the analytical laboratory. According to Greenway et al. (2010) the reference range for serum LCM monitoring is considered to be 10–20 mg/L. Pedersen and Rasmussen (2013) suggested that there could be a therapeutic interval for LCM from 3–8.8 mg/L.

Finally, we have to discuss if the favourable outcome was related to LCM or whether it occurred spontaneously or accidentally. Epidemiologic studies suggest the probability of a fluctuating course of drug resistance (Kwan et al., 2011). In the case of M the stopping of seizures and the increase of the LCM dosage were associated so closely that a spontaneous or accidental outcome seems to be not probable. We do not know definitely if LCM would have been as effective if it would have been given as monotherapy; we know, however, that LTG in other combinations (and probably also in monotherapy) was not or not highly effective in this patient in the past. Any significant synergism of LCM and LTG has not been published until now (Fröscher and Rösche 2013; Ben-Menachem, 2014). Perhaps, at an earlier stage of the disease it would have been possible to stop the seizures of M with another AED at a recommended dosage.

CONFLICT OF INTEREST DISCLOSURE
The authors declared no conflict of interests.

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