Epilepsy & Behavior 20 (2011) 20–23

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Lacosamide neurotoxicity associated with concomitant use of sodium channel-blocking antiepileptic drugs: A pharmacodynamic interaction?

Jan Novy [a], Philip N. Patsalos [a], Josemir W. Sander [a,b], Sanjay M. Sisodiya [a,*]

[a] Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
[b] SEIN—Epilepsy Institute in The Netherlands Foundation, Achterweg 5, 2103SW Heemstede, The Netherlands

ARTICLE INFO

Article history:
Received 31 August 2010
Revised 29 September 2010
Accepted 3 October 2010
Available online 5 November 2010

Keywords:
Lacosamide
Interaction
Pharmacodynamics
Sodium voltage-gated channel
Drug load

ABSTRACT

Lacosamide is a new antiepileptic drug (AED) apparently devoid of major pharmacokinetic interactions. Data from a small postmarketing assessment suggest people who had lacosamide co-prescribed with a voltage-gated sodium channel (VGSC)-blocking AED seemed more likely to discontinue lacosamide because of tolerability problems. Among 39 people with refractory epilepsy who developed neurotoxicity (diplopia, dizziness, drowsiness) on lacosamide treatment given in combination with VGSC-blocking AEDs, we identified 7 (17.9%) without any changes in serum levels of other AEDs in whom the symptoms were ameliorated by dose reduction of the concomitant VGSC-blocking AED. Symptoms in these people seem to have arisen from a pharmacodynamic interaction between lacosamide and other VGSC-blocking AEDs. Slow-inactivated VGSCs targeted by lacosamide might be more sensitive to the effects of conventional VGSC-blocking AEDs. Advising people to reduce concomitantly the conventional VGSC-blocking AEDs during lacosamide uptitration in cases of neurotoxicity might improve the tolerability of combination treatment.

1. Introduction

Lacosamide was recently licensed as an add-on antiepileptic drug (AED) for partial epilepsy. Clinical trial data suggest it has a response rate (>50% reduction in seizure frequency) of 35–41% at doses between 400 and 600 mg daily [1–3]. Oral lacosamide is almost completely absorbed and reaches its maximal concentration within 1 to 4 hours, with a half-life of 13 hours [4]. It has a favorable pharmacokinetic profile, as it is mostly excreted unchanged in urine. It has minor hepatic metabolism (cytochrome P450 2C19), but displays no significant pharmacokinetic interaction [5,6]. Lacosamide was shown to act by enhancing slow inactivation of voltage-gated sodium channels (VGSCs), believed to be a new mechanism of action, as other VGSC-blocking AEDs (carbamazepine, phenytoin, lamotrigine, oxcarbazepine) act on fast inactivation [7]. Lacosamide also binds to CRMP-2, an intracellular signal protein involved in neuronal differentiation and growth [8]. This putative mechanism, which was also recently suggested to modulate its action on VGSCs [9], is still debated.

Lacosamide is generally well tolerated, with mostly dose-dependent central nervous system side effects (dizziness, diplopia, blurred vision, somnolence, or headache) [3]. In a postmarketing series of 25 people treated with lacosamide, 3 concomitantly taking other VGSC-blocking AEDs discontinued treatment because of side effects, but it was assumed that this was not due to an interaction between the AEDs [10].

We report a series of seven people with epilepsy who experienced significant neurotoxicity during the introduction of lacosamide in association with other VGSC-blocking AEDs, and our data suggest this is likely to be due to a pharmacodynamic interaction.

2. Case reports

We reviewed the notes of all the people seen by two clinicians at specialized epilepsy clinics of the National Hospital for Neurology and Neurosurgery who reported neurotoxicity events (45 individuals). None of 6 people on lacosamide in combination with other non-VGSC-blocking AEDs experienced such an interaction. Among 39 people experiencing neurotoxicity on a combination of lacosamide and other VGSC-blocking AEDs, 9 experienced an interaction between lacosamide and VGSC-blocking AEDs; 2 of these were excluded as there were insufficient drug level data.

The demographics, diagnoses, and previous AED medications for the seven people reported are summarized in Table 1. AED serum levels are detailed in Table 2.

2.1. Case 1

On levetiracetam (2500 mg daily), oxcarbazepine (1800 mg), and clobazam (10 mg), this woman continued to experience monthly seizures. She started lacosamide and the dose was increased over 2 months to 200 mg/day. There was a significant decrease in seizure

* Corresponding author. Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK.
E-mail address: s.sisodiya@ion.ucl.ac.uk (S.M. Sisodiya).

1525-5050/$ – see front matter

Table 1
Demographics, diagnosis and previous antiepileptic medication of the patients.

Case	Diagnosis	Previously tried antiepileptic drugs
1. Female, age 26	Symptomatic epilepsy with complex partial and generalized seizures Left periventricular heterotopia	Lamotrigine
2. Male, age 22	Cryptogenic right frontal epilepsy with complex partial and generalized tonic–clonic seizures	Valproate, levetiracetam topiramate, zonisamide, topiramate
3. Female, age 37	Cryptogenic frontal lobe epilepsy with complex partial seizures, generalized tonic–clonic seizures, and drop attacks	Carbamazepine, valproate, acetazolamide gabapentin, topiramate, felbamate, levetiracetam oxcarbazepine, zonisamide, tiagabine, phenobarbital
4. Female, age 77	Cryptogenic partial epilepsy with complex partial seizures	Lamotrigine, carbamazepine, levetiracetam
5. Female, age 24	Multifocal epilepsy with simple and complex partial seizures Learning disability and dysmorphism (4p trisomy)	Valproate, topiramate, clobazam valproate, topiramate, gabapentin, clobazam
6. Female, age 36	Symptomatic epilepsy with partial seizures Resection and radiotherapy of low-grade astrocytoma Communicating hydrocephalus with ventriculoperitoneal shunt	Carbamazepine, valproate, vigabatrin lamotrigine, gabapentin, phenobarbital
7. Female, age 47	Symptomatic epilepsy with simple partial and generalized seizures Right temporoparietal dysplasia	Phenobarbital, phenytoin, topiramate, vigabatrin, carbamazepine, valproate, clobazam, acetazolamide, lamotrigine, methsuximide, felbamate, gabapentin, tiagabine

frequency, but when the dose of 200 mg/day was reached, she experienced recurrent episodes of diplopia and ataxia. Serum levels of concomitant AEDs did not show any significant change after the introduction of lacosamide. Serum levels of lacosamide were below the reference range [11]. As seizure frequency had decreased significantly, oxcarbazepine was reduced to 1500 mg with improvement of the symptoms, allowing the gradual increase in lacosamide up to 300 mg/day over 4 weeks. Symptoms recurred when she reached 300 mg/day, alleviated by a further decrease in oxcarbazepine to 1350 mg. She continued to have significant seizure reduction and was able to increase lacosamide to 350 mg/day without additional adverse events.

2.2. Case 2

On carbamazepine retard 1800 mg per day, this man continued to have two seizures weekly. Lacosamide was started with a view toward increasing the dose to 200 mg/day over 6 weeks. It was well

Table 2
Serum levels of the antiepileptic drugs.

Case	Antiepileptic drug/metabolite	Serum level (μmol/L)		
		Before lacosamide introduction	At the time of the symptoms	After VGSC-blocking AED reduction
1	10-Hydroxycarbazepine	103	108	–
	Levetiracetam	161	197	–
	Lacosamide	–	21	–
2	Carbamazepine	47.7	49.8	–
	Carbamazepine epoxide	4.2	4.8	–
	Lacosamide	–	5	–
3	Phenytoin	80 (1 h after dosing)	99 (3 h after dosing)	89 (3 h after dosing)
	Lamotrigine	8 (1 h after dosing)	13 (3 h after dosing)	11 (3 h after dosing)
	Lacosamide	-	29 (3 h after dosing)	20 (3 h after dosing)
4	10-Hydroxycarbazepine	74	70	–
	Lacosamide	–	44	–
5	Carbamazepine	46	41	–
	Carbamazepine epoxide	11.5	11.1	–
	Levetiracetam	477	371	–
	Lacosamide	–	48	–
6	10-Hydroxycarbazepine	104	71 (after 150 mg/day reduction)	–
	Topiramate	22	22	–
	Phenytoin	16	9	–
	Lacosamide	–	11	–
7	10-Hydroxycarbazepine	60 (8 h after last dosing)	43 (2 h after last dosing)	47 (8 h after last dosing)
	Levetiracetam	177	154	–
	Lacosamide	–	–	17 (increased to 200 mg/day)

Note. When sampling times after the last dosing differ between the blood samples, they are detailed after the result. Reference ranges used for the AEDs and their metabolites are as used by the Therapeutic Drug Monitoring Unit, National Hospital for Neurology and Neurosurgery, and based on published consensus [18]: 10-hydroxycarbazepine, 50–110;

tolerated up to 100 mg/day, but he could not increase the dose further as he developed blurred vision, dizzy spells, and decreased alertness. These started typically half an hour after drug intake and lasted up to 2 hours. Carbamazepine levels did not change significantly and lacosamide was below the reference range. As the response was encouraging (he had not had any generalized seizures since starting lacosamide), carbamazepine was decreased to 1200 mg/day, leading to symptom resolution. Lacosamide was increased to 200 mg/day without recurrence of the symptoms. He continued to show significant improvement in seizure frequency.

2.3. Case 3

This woman was admitted for seizure control as she was having several disabling seizures a week. She was on phenytoin 375 mg, lamotrigine 500 mg, rufinamide 1000 mg, and clonazepam 2 mg daily. Rufinamide was tapered and lacosamide started and increased up to 200 mg over 4 weeks. At this stage, she developed marked unsteadiness and diplopia about 2 hours after taking her medication. Lamotrigine reduction to 450 mg/day led to a marginal improvement in the dizziness. Serum levels 1 week after lamotrigine reduction showed a phenytoin level above the reference range, as previously, a lamotrigine level within the reference range, and a lacosamide level below the reference range. Phenytoin was decreased to 325 mg/day. Three weeks later, serum levels showed a small decrease in the phenytoin level, though still higher than the upper limit of the reference range. There were no significant changes in serum levels of the other AEDs. This last change reduced the symptoms and she had a slight decrease in seizure frequency.

2.4. Case 4

This woman had daily seizures on oxcarbazepine (750 mg daily) when she started lacosamide. When she reached 300 mg/day in two divided doses, she experienced severe diplopia, mostly after her evening medication. The serum 10-hydroxycarbazepine level did not show significant changes; lacosamide was within the reference range. As there was a significant decrease in seizure frequency, oxcarbazepine was decreased to 600 mg/day which led to complete resolution of the symptoms; she reduced the oxcarbazepine dose further on her own to 300 mg/day. On this combination, she did well and had a significant decrease in seizure frequency.

2.5. Case 5

On carbamazepine 900 mg and levetiracetam 3000 mg daily, this woman was having several seizures per week. Lacosamide was started and slowly increased, leading to a significant decrease in seizures, but when she reached 350 mg/day, 4 months later, she developed severe drowsiness in the morning after drug intake. Her morning carbamazepine dose was reduced to 100 mg (previously 300 mg), which improved the sleepiness but she remained unsteady and dysarthric. Her serum levels did not show any major changes; lacosamide level was within the reference range. Further reduction of carbamazepine led to resolution of symptoms.

2.6. Case 6

On phenytoin (150 mg), oxcarbazepine (1350 mg), and topiramate (250 mg) daily, this woman was continuing to have several seizures per week and was admitted for evaluation and drug changes. She was started on lacosamide. After 2 weeks when she reached 100 mg/day, she developed diplopia and unsteadiness. Oxcarbazepine was decreased by 150 mg to 1200 mg/day which led to only a minimum improvement in symptoms. One week later, symptoms continued: level and no significant changes in topiramate and phenytoin levels; the lacosamide level was below the reference range. Oxcarbazepine was reduced gradually over 3 weeks to 300 mg daily which alleviated the symptoms and allowed concomitant increase in lacosamide up to 200 mg daily. A mild reduction in seizure frequency was observed during her stay.

2.7. Case 7

This woman with weekly seizures was admitted for drug changes on clonazepam (1.5 mg daily), oxcarbazepine (1500 mg), diazepam (4 mg), and levetiracetam (4000 mg). She started on lacosamide and when she reached 100 mg/day, 2 weeks later, she developed diplopia, ataxia, and vertigo. Serum levels did not show major changes despite collection of blood at different times; lacosamide was not measured at that time but was below the reference range 1 month later while she was on 200 mg/day. As she had a reduction in seizures, oxcarbazepine was decreased to 1200 mg/day and the symptoms resolved; the 10-hydroxycarbazepine level showed a small fall. Lacosamide was further increased to 200 mg without any side effects and she continued to experience a favorable response to the treatment.

In the same clinics, we identified six additional people with neurotoxicity on lacosamide who were not taking VGSC-blocking AEDs. We calculated the total drug load for all people according to Deckers et al. [12] (sum of the ratio of prescribed daily dose and usual daily dose defined by the World Health Organization). At the time of symptoms, the mean value was 2.9 (range: 0.5–6.6) for the 37 people for whom there were sufficient data and who were on lacosamide and another VGSC-blocking AED and 2.3 (range: 1.6–2.9) for the 6 individuals on lacosamide without any other VGSC-blocking AED ($P = 0.41$, Kruskal–Wallis test; SPSS Version 18). For the seven cases described above, the mean drug load was 3.3 and the mean change in drug load to alleviate the symptoms was 0.24 (range: 0–0.7).

3. Discussion

We report a series of seven people with refractory epilepsy who experienced significant central nervous system side effects (mostly dizziness, imbalance, diplopia, and sedation) on the introduction of lacosamide in combination with other VGSC-blocking AEDs. In some, the symptoms occurred shortly after drug intake (0.5–2 hours), compatible with peak serum levels. These symptoms occurred as lacosamide was at a low to medium dose (100–350 mg daily) and lacosamide levels were below or at the lower limit of the reference range. As previously reported [5,6], we did not find any convincing pharmacokinetic interaction, with no significant changes in concentrations of concomitant AEDs. Reduction of the load of VGSC-blocking AEDs seemed to alleviate the symptoms, allowing further titration of lacosamide, which may suggest a pharmacodynamic interaction. Such an interaction was not found in a study involving healthy volunteers, perhaps because the combination of drugs was used only shortly (1 week) [6]. We cannot completely exclude a drug load effect in these people; however, their symptoms (such as diplopia) were suggestive of VGSC-blocking AEDs and not typical of other concomitant AEDs such as levetiracetam and topiramate. As reported previously [10], we found that a larger number of people experienced neurotoxicity when lacosamide was added to another VGSC-blocking AED than when it was added to a non-VGSC-blocking AED (39 people vs 6 people). The comparison of drug load among people on lacosamide and another VGSC-blocking AED as compared with six controls (on lacosamide with non-VGSC-blocking AEDs) was not conclusive, probably owing to the small number of controls. In the seven individuals described, the drug load change to alleviate their symptoms was small (−0.24) and none had to discontinue any of their drugs. Two people (cases 1 and 7) did not require a decrease in their

of the 38 other people (on other VGSC-blocking AEDs or non-VGSC-blocking AEDs) experiencing neurotoxicity, a reduction in the concomitant AEDs did not alleviate the symptoms and lacosamide had to be reduced or stopped, which might suggest that the seven people discussed here experienced a specific interaction.

The mechanism of this possible interaction might be explained by the common target (VGSC) of lacosamide, carbamazepine, oxcarbazepine, lamotrigine, and phenytoin. Lacosamide selectively enhances entry of VGSC into the unavailable slow-inactivated state (physiologically triggered by prolonged membrane depolarization), in contrast to conventional VGSC-blocking AEDs which act by enhancing fast inactivation [7]. On the basis of their in vitro properties, no interaction between lacosamide and the other VGSC-blocking AEDs was foreseen [7]. In fact, the binding site of carbamazepine and phenytoin on the VGSC is better known [13,14] than that of lacosamide, about which it is only known that it weakly displaces batrachotoxin from its binding site [15]. Recently, it was suggested that its action on the VGSC might be indirectly mediated through binding to CRMP-2 [9]. VGSC in the slow inactivation state (enhanced by lacosamide), however, has been shown to undergo a conformational change of its outer ring [16]. One explanation for this interaction might thus be that the conformational shift favored by lacosamide leads to increased VGSC affinity for binding other AEDs. Supporting this hypothesis, in rat dorsal root ganglion cells, blockade of sodium current mediated by carbamazepine was shown to be increased by the proportion of VGSC in the slow inactivated state. It was hypothesized that the drug might bind to a high-affinity site on the slow inactivated VGSC [17]. In the same experiment, carbamazepine was also shown to slow the return of the VGSC from the slow inactivated state to a normal available state, which might enhance the effects of lacosamide. VGSCs might become more sensitive to VSGC-blocking AEDs because of the effects of lacosamide, such that a subsequent reduction of the concomitant VGSC-blocking AED might restore the previous binding rate and improve tolerability. This would also explain why we did not observe any increase in seizure frequency after reduction of the concomitant VGSC-blocking AED. In our series, the combination of lacosamide with another VGSC-blocking AED was successful in reducing seizures, but our series was small and selected. Indeed, the reduction of the other VGSC-blocking AED was attempted as lacosamide had proven efficacious, but had this not been the case, lacosamide would have been stopped because of these side effects, without data on a potential pharmacodynamic interaction.

This interaction could be demonstrated at least in 17.9% of people reporting neurotoxicity with the co-prescription of lacosamide and other VGSC-blocking AEDs. Two other people with symptoms also suggestive of this interaction were excluded as a pharmacokinetic interaction could not be excluded. Our series consisted of people who had an early encouraging response to the treatment, suggesting that the real prevalence of this interaction might be greater than suggested here.

From a practical perspective, a stepwise progressive reduction in carbamazepine, oxcarbazepine, phenytoin, or lamotrigine (as needed) could be part of the regime for people starting lacosamide in association with these AEDs; as in our patients, a moderate reduction (13–55% of the total dosage) was able to relieve symptoms. Alternatively, this could be undertaken when symptoms occur and lacosamide has been shown to be effective. In our series, some patients were then able to increase lacosamide further without recurrence of the side effects, whereas others needed further reduction of the other AED along with an increase in lacosamide. The use of such titration might improve lacosamide tolerability. This titration might thus help to avoid inappropriate withdrawal of a useful drug because of perceived lacosamide-related side effects. Our data suggest that the early appearance of neurotoxicity during the introduction of lacosamide with another VGSC-blocking AED may possibly be caused by a pharmacodynamic interaction. The frequency of this interaction is probably higher than demonstrated here (17.9%), but may be mostly encountered in people responding to lacosamide in clinical practice.

Acknowledgments

This work was undertaken at UCLH/UCL, which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. Dr. Novy is supported by the Swiss National Science Foundation Fellowships for Prospective Researchers.

References

[1] Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, et al. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia 2009;50:443–53.
[2] Chung S, Sperling MR, Biton V, et al. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. Epilepsia 2010;51:958–67.
[3] Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia 2007;48:1308–17.
[4] Horstmann R, Bonn R, Cawello W, Doty P, Rudd D. Basic clinical pharmacologic investigations of the new antiepileptic drug SPM 927. Epilepsia 2002;43(Suppl 7): 188.
[5] Johannessen Landmark C, Patsalos PN. Drug interactions involving the new second- and third-generation antiepileptic drugs. Expert Rev Neurother 2010;10: 119–40.
[6] Cawello W, Nickel B, Eggert-Formella A. No pharmacokinetic interaction between lacosamide and carbamazepine in healthy volunteers. J Clin Pharmacol 2010;50: 459–71.
[7] Errington AC, Stohr T, Heers C, Lees G. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. Mol Pharmacol 2008;73:157–69.
[8] Beyreuther BK, Freitag J, Heers C, Krebsfanger N, Scharfenecker U, Stohr T. Lacosamide: a review of preclinical properties. CNS Drug Rev 2007;13:21–42.
[9] Wang Y, Brittain JM, Jarecki BW, et al. In silico docking and electrophysiological characterization of lacosamide binding sites on collapsin response mediator protein 2 (CRMP-2) identifies a pocket important in modulating sodium channel slow inactivation. J Biol Chem 2010;285:25296–307.
[10] Wehner T, Bauer S, Hamer HM, et al. Six months of postmarketing experience with adjunctive lacosamide in patients with pharmacoresistant focal epilepsy at a tertiary epilepsy center in Germany. Epilepsy Behav 2009;16:423–5.
[11] Greenaway C, Ratnaraj N, Sander JW, Patsalos PN. A high-performance liquid chromatography assay to monitor the new antiepileptic drug lacosamide in patients with epilepsy. Ther Drug Monit 2010;32:448–52.
[12] Deckers CL, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. Epilepsia 1997;38: 570–5.
[13] Kuo C-C. A common anticonvulsant binding site for phenytoin, carbamazepine, and lamotrigine in neuronal Na^+ channels. Mol Pharmacol 1998;54:712–21.
[14] Tate SK, Depondt C, Sisodiya SM, et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proc Natl Acad Sci USA 2005;102:5507–12.
[15] Errington AC, Coyne L, Stohr T, Selve N, Lees G. Seeking a mechanism of action for the novel anticonvulsant lacosamide. Neuropharmacology 2006;50:1016–29.
[16] Xiong W, Li RA, Tian Y, Tomaselli GF. Molecular motions of the outer ring of charge of the sodium channel. J Gen Physiol 2003;122:323–32.
[17] Cardenas CA, Cardenas CG, de Armendi AJ, Scroggs RS. Carbamazepine interacts with a slow inactivation state of NaV1.8-like sodium channels. Neurosci Lett 2006;408:129–34.
[18] Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239–76.