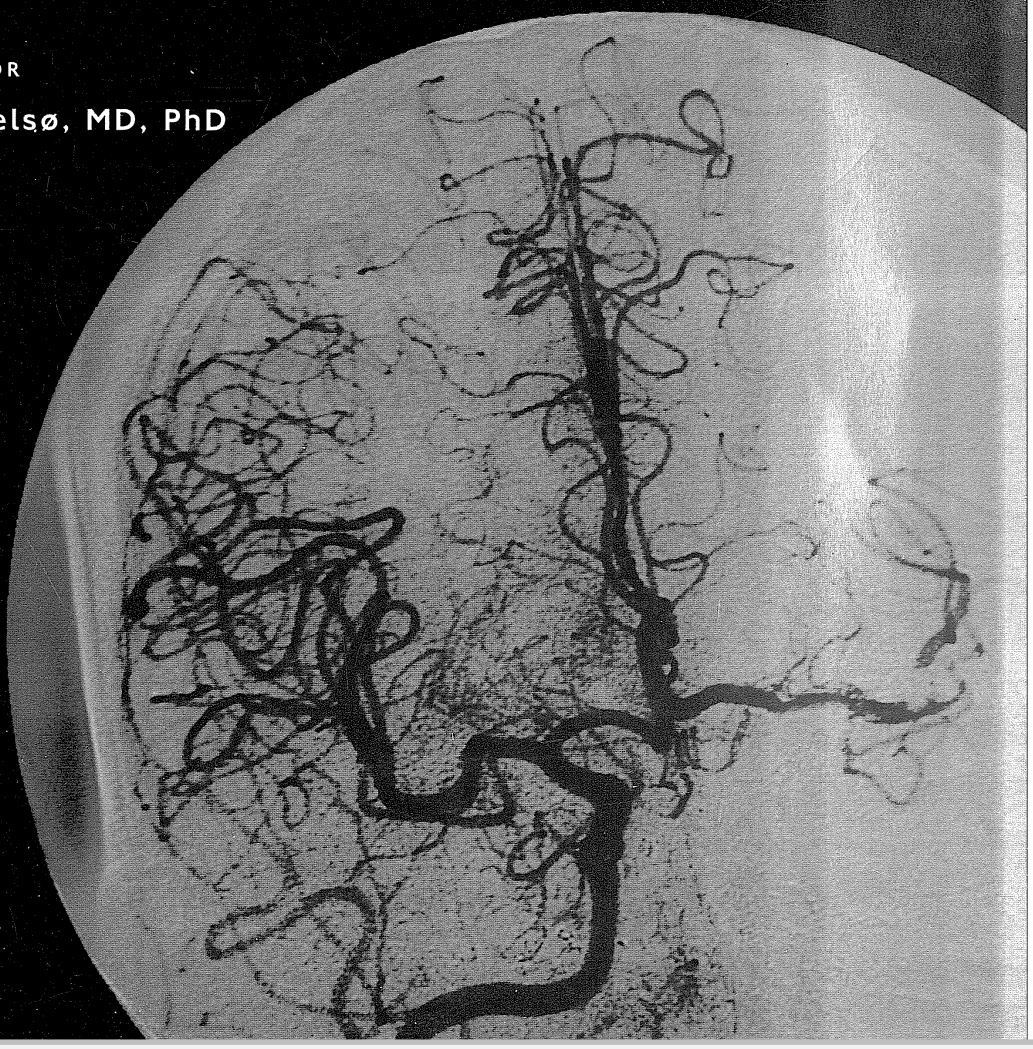
VOLUME 127 • MARCH 2013 • NUMBER 3

FOUNDED IN 1926

Acta Neurologica Scandinavica



WILEY
Blackwell

Acta Neurol Scand 2013: 127: 149–153 DOI: 10.1111/j.1600-0404.2012.01704.x

ACTA NEUROLOGICA SCANDINAVICA

Clinical experience with using lacosamide for the treatment of epilepsy in a tertiary centre

Kamel JT, DeGruyter MA, D'Souza WJ, Cook MJ. Clinical experience with using lacosamide for the treatment of epilepsy in a tertiary centre.
Acta Neurol Scand: 2013: 127: 149–153.

Objective – Lacosamide is approved for the adjunctive treatment of partial-onset seizures in adults. Phase II/III clinical trials suggest that it is a safe, effective and well-tolerated medication. However, there is little post-marketing information available about this medication. *Methods* – We report our clinical experience from a tertiary referral epilepsy centre, which has been using lacosamide for the past 18 months, with 128 patients treated during this time. *Results* – Fifty-three patients (41%) achieved at least a 50% reduction in seizure frequency, with 14 patients (11%) achieving seizure freedom for a mean time of 35 weeks. This 50% responder rate matches, and the seizure free rate outperforms that seen in previous pooled trials. The efficacy of lacosamide did not vary with concurrent sodium channel blocking agent (SCB) use, and a statistically significant dose-dependent response was not shown, which is in contrast to previous trials. Treatment emergent adverse effects (TEAEs) were noted in 52 patients (41%), with 24 patients (19%) discontinuing the medication. TEAEs were more frequent in patients on concurrent SCBs, affecting 51% vs. 28% of patients not on other SCBs. This increased risk of TEAEs from concurrent SCB use was of statistical significance ($P = 0.01$). The most frequently noted TEAEs from lacosamide were dizziness, sedation and diplopia, which all appeared to be dose-related. *Conclusion* – This post-marketing analysis suggests that lacosamide in clinical practice at least mirrors, and possibly outperforms the results seen in previous phase II/III trials.

J. T. Kamel, M. A. DeGruyter, W. J. D'Souza, M. J. Cook

The Department of Medicine, St. Vincent's Hospital Melbourne, The University of Melbourne, Fitzroy, Melbourne, Australia

Key words: antiepileptic drugs; lacosamide; lamotrigine; sodium channel blocking agent

J. T. Kamel, The Department of Neurology and Neurological Research, The Department of Medicine, St. Vincent's Hospital Melbourne, PO Box 2900, Fitzroy, Melbourne, Vic 3065, Australia
Tel.: +61 3 9288 2211
Fax: +61 39 288 4871
e-mail: jordan.kamel@svhm.org.au

Accepted for publication June 20, 2012

Introduction

Lacosamide is a new antiepileptic drug (AED), which is approved for the adjunctive treatment of partial-onset seizures in adults. It selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation. This may make it more selective than older generation AEDs, such as phenytoin and carbamazepine, for repeatedly depolarizing neurons of seizure activity (1). Other favourable aspects of lacosamide include its pharmacokinetic profile, with high oral bioavailability of approximately 100%, twice-daily dosing with a relatively long elimination half-life of 13 h, linear pharmacokinetics and renal elimination (2). It has minimal binding to plasma proteins, has no known clinically relevant drug–drug interactions (3), and does not induce or inhibit enzymes of the cytochrome P450 system (4). In addition, cost utility results have shown that lacosamide is a cost-effective treatment for uncontrolled partial-onset seizures (5).

Although there are no pharmacokinetic interactions with the more traditional voltage-gated sodium channel blockers (SCBs), such as carbamazepine and phenytoin (6), it has been suggested that neurotoxicity with lacosamide may be more

likely with concomitant use through pharmacodynamic effects. The central adverse effects of drowsiness, dizziness and diplopia may be ameliorated by dose reduction of the other SCB (7).

Previous phase II/III clinical trials suggest that lacosamide is a safe, effective and well-tolerated medication (8). However, there is very little post-marketing experience available in the current literature, with only a handful of such analyses reported to date (9, 10). Our tertiary epilepsy centre has been using lacosamide for the past 18 months, with 128 patients treated during this time. We report our experiences with efficacy, tolerability and side effects of this medication.

Methods

At a tertiary epilepsy centre, a total of 128 patients were commenced on lacosamide between December 2009 and April 2011. The dose was started at 50 mg twice daily and titrated up as guided by the treating epileptologist. The data of this group of consecutive patients were collected and analysed retrospectively, primarily through access to patient notes and medical records.

The efficacy on seizure frequency reduction once a maintenance dose was reached was categorized as 100% response, >50% response, <50% but >0% response, no effect, or worsening of seizure frequency. This was routinely enquired about by the treating epileptologist and recorded in the patient's medical notes. In addition, patients were encouraged to keep seizure diaries. Efficacy of lacosamide $\leq$200 mg/day was compared to >200 mg/day for statistical significance, using Fisher's exact test. Doses higher than 200 mg/day were grouped together in assessment of efficacy, because of the low sample size in patients on these doses.

The tolerability of lacosamide was assessed by routinely asking patients of any potential treatment emergent adverse effects (TEAEs) that were noted after commencing the medication. Concurrent AEDs were noted, and patients were grouped according to those that were taking at least one traditional SCB (which included phenytoin, primidone, carbamazepine and oxcarbazepine), and those that were not. Although lamotrigine does exert a therapeutic effect through inhibiting sodium channels, for all intensive purposes regarding its pharmacodynamic actions through other pathways and side effect profile in general, it was considered by the authors to be considered as a non-SCB. The statistical significance of TEAE incidence between patient groups according to concurrent SCB use, as well as differences in efficacy, was analysed using Fisher's exact test.

Results

A total of 128 patients were commenced on lacosamide. About119 had symptomatic focal epilepsies. Surgical candidates were not excluded. There were also nine patients that had idiopathic generalized epilepsies; in several of these cases, the patients in this group were commenced on lacosamide when their epilepsies were thought to be of a focal nature, but later proven to be generalized. Given this small sample size, patients with IGE were unable to be analysed separately. The 71 (55%) of patients were on at least one traditional SCB. The dosage of lacosamide ranged from 100 to 500 mg daily. The baseline characteristics of our patients and lacosamide usage are outlined in Table 1.

Fifty-three patients (41%) achieved at least a 50% reduction in seizure frequency (50% responder rate), with 14 patients (11%) achieving complete seizure remission. The average time our patients have been seizure free on lacosamide is 35 weeks, which is longer than the 12-week Maintenance Phase used to assess patients in past phase II/III clinical trials. There were 44 patients (34%) that did not note any reduction in their seizure frequency. This is represented in Fig. 1. No patients noted worsening of their seizures after commencement of lacosamide. Fig. 1 also includes efficacy data according to lacosamide dose and concurrent SCB use.

Higher dosages of lacosamide were not superior to lower dosages in our cohort of patients. Although there was a slightly higher percentage of patients who experienced seizure freedom (12% vs

Table 1 Baseline characteristics of patients on lacosamide

Age (mean, years)	39 (range 18–72)
Female	64 (50%)
Duration on lacosamide (mean)	7 months (range 1–17)
Dosage	
$\leq$200 mg/day	79 (61.7%)
>200 and $\leq$ 300 mg/day	29 (22.6%)
>300 and $\leq$ 400 mg/day	19 (14.8%)
>400 mg/day	1 (0.8%)
Mean dose	250 mg/day
Patients on concomitant SCBs	71 (55%)
No. of concomitant AEDs	
0	1 (1%)
1	9 (7%)
2	35 (27%)
3	52 (41%)
4	26 (20%)
5	5 (4%)

AEDs, antiepileptic drugs; SCBs, sodium channel blockers.

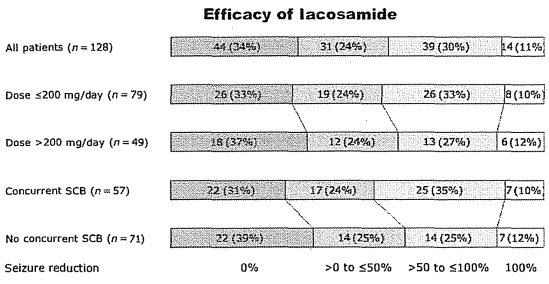


Figure 1. Efficacy of lacosamide.

10%), this was offset by fewer patients achieving >50% seizure reduction (39% vs 43%); overall, there was no statistical significance between the two groups ($P = 0.71$; Fisher's exact test).

The subgroup taking concurrent sodium channel blocking agents had a higher percentage of patients achieving a >50% seizure reduction (45% vs 37%). However, this association did not reach statistical significance ($P = 0.37$; Fisher's exact test).

Treatment emergent adverse effects were noted in 52 patients (41%), with 24 patients (19%) discontinuing the medication, at least in part due to these side effects. TEAEs were more frequent in patients on concurrent SCBs, affecting 51% of patients in this group, compared with those not on other SCBs, affecting 28% of these patients (Table 2). This association between concurrent SCB use and increased risk of adverse effects was of statistical significance ($P = 0.01$; Fisher's exact test).

Treatment emergent adverse effects were reported in 20 of 61 patients (33%) on lamotrigine and 7 of 37 patients (19%) on lamotrigine after excluding those on other concurrent SCBs. Compared to patients on concurrent SCBs and not on lamotrigine, where 23 of 47 patients (49%) experienced TEAEs (Table 3), this difference in risk is of statistical significance ($P < 0.01$; Fisher's exact test). This supports the notion discussed earlier that the pharmacodynamic effect of lamotrigine differs to that of the more traditional SCBs and behaves clinically more like a non-SCB.

The most frequently noted TEAEs were dizziness/ataxia in 26 patients (20%), sedation in 18 patients (14%) and diplopia in 6 patients (5%; see Fig. 2 for all adverse effects noted).

Table 2 Comparison of adverse effects (AEs) between patients on concurrent sodium channel blocking agents (SCB) and those that were not

	AEs (%)	No AEs (%)	Total
SCB	36 (51)	35 (49)	71
No SCB	16 (28)	41 (72)	57
Total	52 (41)	76 (59)	128

$P = 0.01$; Fisher's exact test.

Table 3 Comparison of adverse effects (AEs) between patients on lamotrigine (LTG) and those on concurrent sodium channel blockers (SCB) with lamotrigine excluded

	AEs (%)	No AEs (%)	Total
LTG	7 (19)	30 (81)	37
SCB	23 (49)	24 (51)	47
Total	30 (36)	54 (64)	84

$P < 0.01$; Fisher's exact test.

Discussion

The baseline characteristics of age and gender were very similar to those seen in the populations from pooled analyses of phase II/III clinical trials (11). In these trials, 82% of patients were on at least one other 'traditional' SCB. In our patient group, only 55% were on another SCB. However, it should be noted that these trials included lamotrigine as a SCB, and when accounting for this, the range of concurrent AEDs used is similar. The number of concurrent AEDs used was higher in our group of patients, with significantly more patients taking three or more other AEDs in both SCB and non-SCB groups (Table 1), in comparison with the phase II/III clinical trials patients. The reason for this is unclear, but perhaps reflects the cohort of patients with particular refractory disease being referred to our epilepsy centre.

The 50% responder rate amongst our patients was 41%, which was similar to the pooled analysis results for lacosamide 200 mg/day (50% responder rate of 34.1% intent-to-treat and 34.8% modified ITT), and for lacosamide 400 mg/day (50% responder rate of 39.7% ITT and 44.3% mITT) (8). This suggests that these results from phase II/III trials are at least reproducible in our post-marketing experience.

Interestingly, the 50% responder rate was not significantly different between lower-dose ($\leq$200 mg/day) and higher-dose (>200 mg/day) lacosamide. This is in contrast to previous pooled analysis results discussed, which demonstrate a dose-related treatment response, with 400 mg/day more effective than 200 mg/day (8). Although we had 128 patients in our cohort, when subdivided according to dose, our sample sizes decrease to significantly <200+ patients enrolled in each dosage arm of previous phase II/III trials. This lack of power could potentially account for not finding this dose-related response.

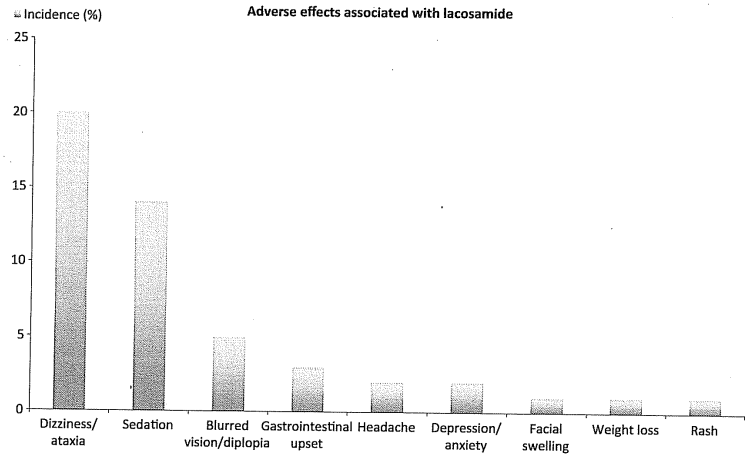


Figure 2. Adverse effects associated with lacosamide.

The 50% responder rate also did not differ according to whether patients were taking concurrent SCBs or not, and this relationship did not show any meaningful statistical significance. Similar findings have been reached by another post-marketing study by Stephen et al. (10).

Of note, 14 of our patients (11%) became seizure free after commencing lacosamide, in comparison with the 2.7% of patients taking lacosamide 200 mg/day and 3.3% of patients taking 400 mg/day in the phase II/III trials who completed the 12-week Maintenance Phase (8). As mentioned in the results section, this is a considerable shorter period than that of our patients.

The increased TEAEs seen in patients on concurrent SCBs compared with those on AEDs with other mechanisms were statistically significant (51% vs 28%, $P = 0.01$). This is in contrast to the study by Stephen et al. (10), which concluded that lacosamide is as well tolerated in patients on traditional SCBs. Our findings are, however, concordant with suggestions by the post hoc analysis of pooled clinical trial data by Sake et al., which suggest that there may be an improved tolerability for lacosamide in patients not on other SCBs.

Despite our patients generally taking more concurrent AEDs, the side effect noted from lacosamide was overall less than that seen in previous trials. One possible reason is that the dosages of lacosamide used in our patients were overall lower than those used in the trials (11), and doses in these trials were more rapidly titrated up in a forced schedule, in comparison with the physician-guided approach used in everyday clinical practice.

Conclusions

Our tertiary epilepsy centre has treated 128 patients with lacosamide. The 50% responder rate was 41%, which includes 11% of patients who became seizure free. This post-marketing experience suggests that lacosamide in clinical practice at least mirrors and possibly outperforms the results seen in previous phase II/III trials. Our study did not demonstrate a dose-dependent efficacy. TEAEs were more frequent in patients on concurrent sodium channel blocking agents.

Acknowledgements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of interest

The preparation of this article was not supported by any external funding. J.T. Kamel has received previous educational support from UCB Pharma. M.A. DeGruyter has no conflict of interest to disclose. W.J. D'Souza has received travel, investigator-initiated and speaker honoraria from UCB Pharma. He has received educational, travel and fellowship grants from GSK neurology Australia. He has received educational grants from Novartis Pharmaceuticals and Pfizer Pharmaceuticals. He has received honoraria from Scigen Pharmaceuticals. M.J. Cook has received travel and speaker honoraria from UCB Pharma, Scigen Pharmaceuticals and Sanofi.

References

1. Curia G, Biagini G, Perucca E, Avoli M. Lacosamide: a new approach to target voltage-gated sodium

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.