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Lacosamide: A Review of Preclinical Properties

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ABSTRACT

Lacosamide (LCM), (SPM 927, (R)-2-acetamido-*N*-benzyl-3-methoxypropionamide, previously referred to as harkoseride or ADD 234037) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. LCM has demonstrated antiepileptic effectiveness in different rodent seizure models and antinociceptive potential in experimental animal models that reflect distinct types and symptoms of neuropathic as well as chronic inflammatory pain. Recent results suggest that LCM has a dual mode of action underlying its anticonvulsant and analgesic activity. It was found that LCM selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation. Furthermore, employing proteomic affinity-labeling techniques, collapsin-response mediator protein 2 (CRMP-2 alias DRP-2) was identified as a binding partner. Follow-up experiments confirmed a functional interaction of LCM with CRMP-2 *in vitro*. LCM did not inhibit or induce a wide variety of cytochrome P450 enzymes at therapeutic concentrations. In safety pharmacology and toxicology studies conducted in mice, rats, rabbits, and dogs, LCM was well tolerated. Either none or only minor side effects were observed in safety studies involving the central nervous, respiratory, gastrointestinal, and renal systems and there is no indication of abuse liability. Repeated dose toxicity studies demonstrated that after either intravenous or oral administration of LCM the adverse events were reversible and consisted mostly of exaggerated pharmacodynamic effects on the CNS. No genotoxic or carcinogenic effects were observed *in vivo*, and LCM showed a favorable profile in reproductive and developmental animal studies. Currently, LCM is in a late stage of clinical development as an adjunctive treatment for patients with uncontrolled partial-onset seizures, and it is being assessed as monotherapy in patients with painful diabetic neuropathy.

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Further trials to identify LCM's potential in pain and for other indications have been initiated.

INTRODUCTION

Although some forms of epilepsy may benefit from surgical treatment and others may not need any treatment at all, most patients with epilepsy require chronic pharmacological therapy (Perucca 1996). In the last decade, several new options for the medical treatment of epilepsy have been introduced, including novel antiepileptic drugs (AEDs) and vagus nerve stimulation. The new AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, pharmacokinetics, and safety profile (Herman and Pedley 1998). However, more than 30% of patients still have inadequate seizure control with currently available AEDs, or experience significant adverse drug effects. Therefore, a need remains for AEDs with improved effectiveness and tolerability (Sander 1998).

A similar situation exists for the treatment of neuropathic pain. The response of neuropathic pain to opioid analgesics is inconsistent, with reports of both effect and lack of effect with morphine, for example (Gimbel et al. 2003). It is now accepted that tricyclic antidepressants such as amitriptyline (Max et al. 1992; McQuay et al. 1996), selective serotonin and norepinephrine reuptake inhibitors such as duloxetine (Goldstein et al. 2005), and AEDs have analgesic activity in neuropathic pain. Among the AEDs, carbamazepine (CBZ), phenytoin (PHT) (Sindrup and Jensen 1999), lamotrigine (LTG) (Eisenberg et al. 2001), gabapentin (Backonja et al. 1998), and pregabalin (Rosenstock et al. 2004) have been shown to possess analgesic activity. However, the response to tricyclic antidepressants and AEDs is inconsistent (Sindrup and Jensen 1999). Furthermore, side effects may be significant and often limit the use of these agents in pain patients (Boulton 2003). Thus, there is a need for more effective and better-tolerated drug treatments for patients with neuropathic pain.

Here we report the preclinical profile of lacosamide (LCM) (SPM 927, (R)-2-acetamido-*N*-benzyl-3-methoxypropionamide, previously referred to as harkoseride or ADD 234037), which is a member of a series of functionalized amino acids. It has been suggested that novel AEDs can be improved in three ways: (1) broader and higher efficacy, (2) better tolerability, and (3) improved pharmacokinetic properties. We will review preclinical data to suggest that LCM fulfills all these properties. LCM is in phase III clinical development for adjunctive treatment for patients with uncontrolled partial-onset seizures, and for monotherapy of patients with painful diabetic neuropathy.

CHEMISTRY

The active drug substance is (R)-2-acetamido-*N*-benzyl-3-methoxypropionamide (Fig. 1). LCM is a white to light yellow crystalline powder with a molecular weight of 250.30 Da. Its solubility in phosphate-buffered saline (PBS, pH 7.5, 25°C) is 20.1 mg/mL.

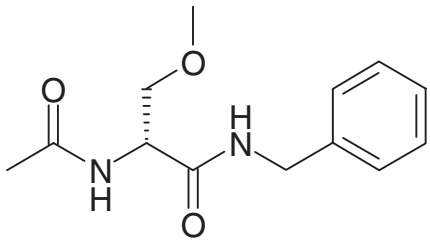

FIG. 1. Chemical structure of lacosamide ($C_{13}H_{18}N_2O_3$).

PHARMACOLOGY

Mode of Action

To unravel the mode of action of LCM, different experimental approaches were followed. In the first step, radioligand binding, electrophysiological, and neurotransmitter release studies were employed to analyze the effects of LCM on general drug targets including well-established mammalian targets for anticonvulsants. Because these experiments did not show a clear effect, two further series of studies were performed to identify the molecular interaction partner: extensive electrophysiological studies on the one hand, and experiments employing affinity-labeling techniques on the other. These studies led to the identification of a novel, dual mode of action for LCM.

Studies on Protein Binding and Neurotransmitter Transport Mechanisms

LCM (10–100 μM) did not significantly bind (>50% inhibition of radioligand binding) to any of more than 100 receptors, channels, or enzymes tested, including molecular targets of other drugs with analgesic and antiepileptic activity (Errington et al. 2006). However, LCM did bind weakly (25–50% inhibition of radioligand binding) to the sodium channel at batrachotoxin site 2. Its major desmethyl metabolite exerted no significant binding to the receptors tested. LCM did not modulate the uptake of the neurotransmitters: norepinephrine, dopamine, or serotonin into synaptosomes, and did not bind to GABA transporters or influence the activity of GABA transaminases.

Effect on Slow Inactivation of Sodium Channels

Voltage-gated sodium channels are responsible for the generation and propagation of action potentials in excitable cells. The excitability of tissues depends mainly on the number of voltage-gated sodium channels that are available for activation. The fraction of sodium channels available for activation is regulated by fast inactivation, which occurs on a millisecond time scale, and slow inactivation occurring within seconds or minutes. Slow inactivation of sodium channels is induced in two different ways (Fig. 2): (1) repeated neuronal firing and/or (2) sustained depolarization from the resting membrane potential (Fleidervish et al. 1996; Mickus et al. 1999; Blair and Bean 2003).

LCM modulates sodium channels in a novel manner: It selectively enhances sodium channel slow inactivation with no effects on fast inactivation. This could be demonstrated in

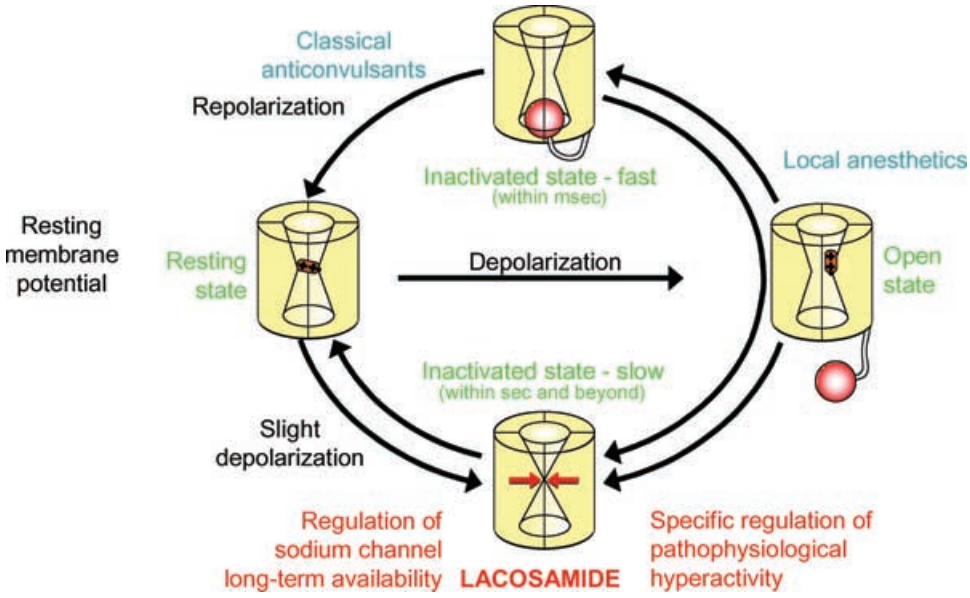

FIG. 2. Physiology of voltage-gated sodium channels. Depending on the membrane potential and the neuronal activity voltage-gated sodium channels are in different states. At the resting potential sodium channels are closed and can be opened by depolarization of the membrane potential allowing the flux of sodium ions into the cell. Within a few milliseconds the channels close from the inside of the neuron and go into the fast inactivated state from which they cannot be activated. When the membrane potential returns to its baseline the sodium channel goes back to its resting state. Under conditions of slight prolonged depolarization and repetitive neuronal activity the sodium channel can go into the slow inactivated state by closing the pore from the inside. This process happens on a second-to-minute time scale. Drugs can either block the open channel (e.g., local anaesthetics), or enhance fast inactivation (classical anticonvulsants) or enhance slow inactivation (lacosamide).

neuroblastoma cells as well as in recombinant neuronal sodium channels expressed in *Xenopus* oocytes or mammalian cells. For example, in neuroblastoma cells LCM concentration dependently shifted the slow inactivation voltage curve to more hyperpolarized potentials and enhanced the maximal fraction of channels, which were slowly inactivated. At the same concentration, LCM had no effect on the voltage dependence of sodium channel fast inactivation. In contrast, the AEDs CBZ, PHT, and LTG shifted V_{50} for fast inactivation to more hyperpolarized potentials (Table 1). The dominant role of fast inactivation for the reduction of sodium current by the anticonvulsants LTG, CBZ, and PHT in contrast to current reduction by LCM is also illustrated in other experiments. When neuroblastoma cells held at a holding potential of −60 mV were depolarized for 10 msec to 0 mV, all drugs tested (LTG, CBZ, PHT, LCM) considerably reduced the fraction of available Na^+ channels (Table 2). However, when fast inactivation was removed by a short prepulse to −100 mV inhibition of sodium current by LTG, CBZ, and PHT was considerably reduced, whereas inhibition by LCM was only minimally affected.

The effect on fast inactivation has been described for some anticonvulsants targeting the sodium channel (Rogawski and Löscher 2004). In addition to its open-channel effect the local anesthetic lidocaine enhances both fast and slow inactivation of sodium channel (Chevrier et al. 2004). The conditions under which slow inactivation is induced, that is, sustained depolarization and for repeated firing, are also relevant in the pathophysiology of

TABLE 1. Effect of anticonvulsants on the voltage dependence of Na^+ channel inactivation.

	Control	Lacosamide	Lamotrigine	Carbamazepine	Phenytoin
Fast inactivation V_{50} [mV]	−66	−65	−72*	−80*	−77*
Slow inactivation V_{50} [mV]	−43	−58*	n.t.	n.t.	n.t.

n.t., not tested. V_{50}, half maximal reduction of channel availability.
All drugs were applied at a concentration of 100 μM. Steady-state fast inactivation was tested with conditioning prepulses of 500 msec between −120 and −20 mV. For steady-state slow inactivation conditioning prepulse duration was 5 sec, followed by a 1-sec hyperpolarizing pulse to −100 mV prior to test pulse to −10mV. $^*P < 0.05$ versus control.

epilepsy and neuropathic pain. Both diseases are characterized by neuronal hyperexcitability mediated by a lowered activation threshold and/or an exaggerated responsiveness of neurons. The mechanisms underlying hyperexcitability are not yet fully understood, but they appear to involve changes in the expression level and pattern of sodium channel isoforms, altered channel-gating kinetics, and reduced input by inhibitory neurons (Devor 2006; Kobayashi et al. 2003).

Neurons within an epileptic focus and neurons after induction of neuropathies can become slightly depolarized as compared to the resting membrane potential of "normal" neurons. This reduced resting membrane potential can be the cause of the reduced activation threshold as observed in "epileptic" or "neuropathic" neurons. As indicated previously, slow inactivation of sodium channels can be powerfully induced by sustained depolarization, and small changes of the resting membrane potential can have large effects on the fraction of sodium channels in the slow inactivated state. Thus it can be expected that some sodium channels are already slowly inactivated under these pathological conditions. However, this might not be sufficient to compensate for increased excitability in diseased tissue. LCM seems to enhance this endogenous adaptation by promoting the transition of sodium channels into the slow inactivated state (i.e., at a given voltage a higher fraction of sodium channels is inactivated) by shifting the voltage dependence of inactivation to more hyperpolarized membrane potentials. However, it does not affect the recovery from slow inactivation. Exaggerated responsiveness of neurons, that is, a given stimulus induces a greater neuronal response than under control conditions, can be attenuated by LCM, because by enhancing slow inactivation it reduces the long-term availability of sodium channels for activation.

The enhancement of slow inactivation of sodium channels by LCM is a novel manner to modulate sodium channels. It can lead to normalization of activation thresholds and a

TABLE 2. Inhibition of Na^+ current with and without removal of fast inactivation.

	Lacosamide	Lamotrigine	Carbamazepine	Phenytoin
% Inhibition of Na^+ current with fast inactivation	32	50	71	48
% Inhibition of Na^+ current after removal of fast inactivation	29	12*	6*	1*

Availability of Na^+ channels was determined in neuroblastoma cells by a 10-msec test pulse to 0 mV from a holding potential of −60 mV. Fast inactivation was removed by a hyperpolarizing pulse to 100 mV (500 msec) prior to the 10-msec test pulse. Concentration of drug was 100 μM for all compounds. $^*P < 0.05$ versus % inhibition with fast inactivation.

reduced pathophysiological hyperresponsiveness, thereby effectively controlling neuronal hyperexcitability without affecting physiological activity.

Effects on CRMP-2

Employing proteomic affinity-labeling techniques, collapsin-response mediator protein 2 (CRMP-2 alias DRP-2, dihydropyrimidinase-related protein) was identified as a binding partner. In subsequent radioligand binding experiments LCM exhibited a binding affinity of 5 μM to this protein. The CRMP family of proteins is implicated in developmental processes of the nervous system, since most of the five CRMP proteins are highly expressed during early development and mainly in the central nervous system. On an *in vitro* level, CRMP-2 has been shown to be involved in neuronal differentiation, polarization, and axonal outgrowth induced by neurotrophic factors such as brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3) (Yoshimura et al. 2005). LCM was shown to interfere with these effects of CRMP-2 in functional studies where LCM inhibited the CRMP-2-mediated effects of neurotrophins (NTs) on axonal outgrowth of primary hippocampal cells with significant effects seen at concentrations starting with 1 μM (Fig. 3).

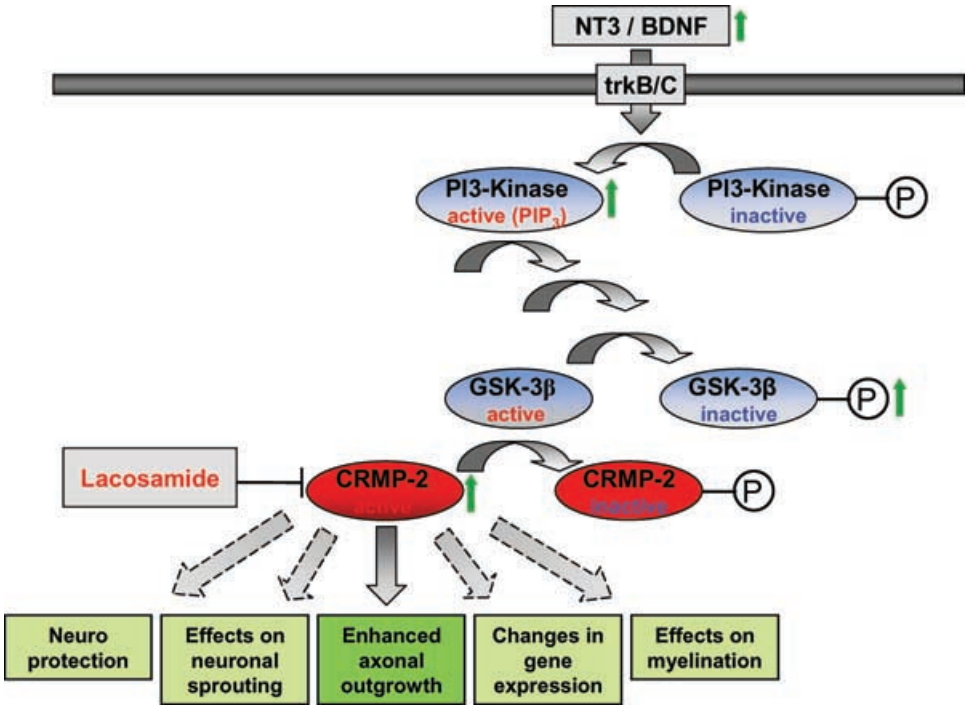

FIG. 3. Schema showing CRMP-2-mediated transduction of neurotrophic signals to neuronal response and the possible interaction of lacosamide. Neurotrophins like NT-3 and BDNF activate their receptors in the plasma membrane, triggering a transduction cascade, which regulates the activity of intracellular protein kinases (e.g., PI3 kinase or GSK-3β) finally resulting in increased levels of active CRMP-2. Active, nonphosphorylated CRMP-2 has been shown to enhance axonal outgrowth and might also be involved in the induction of other cellular responses. Interaction site of lacosamide is indicated.

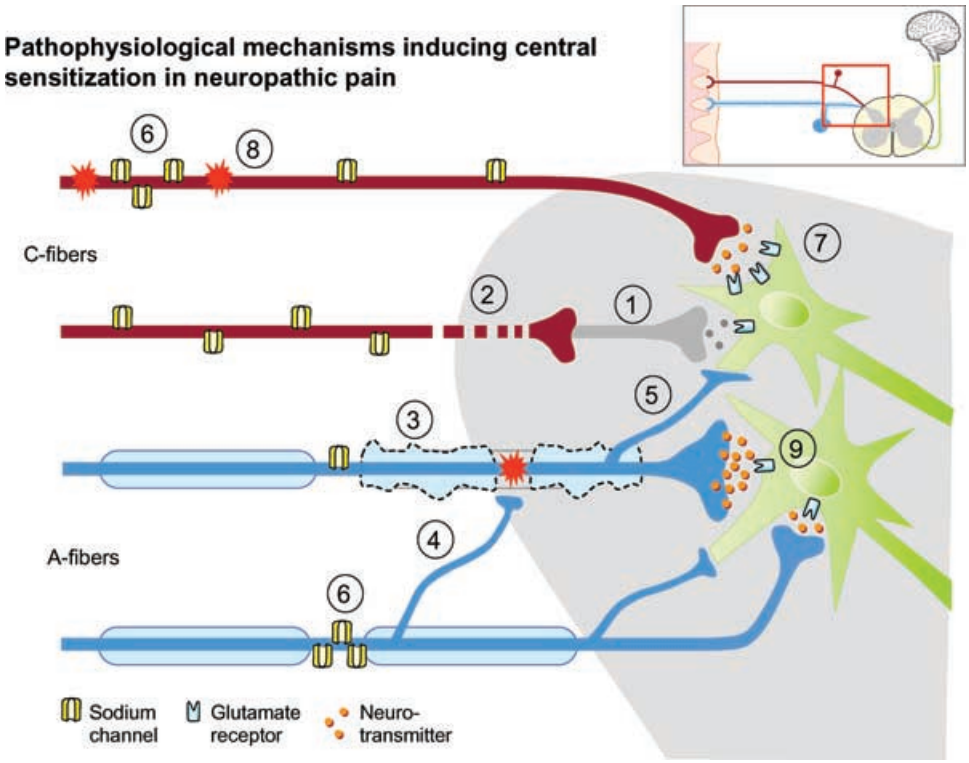

FIG. 4. Pathophysiological mechanisms inducing central sensitization in neuropathic pain. Under conditions of neuropathic pain a cascade of pathophysiological processes is induced: Neuronal loss including neurite retraction (1), neurodegeneration (2) and demyelination (3), neuronal rearrangements including ephapse (4) and sprouting (5) as well as changes in gene expression, for example, of sodium channels (6) or glutamate receptors (7), finally resulting in ectopic firing (8) and enhanced transmission of pain signals (9).

Interestingly, rearrangement of neuronal connections and erroneous neuronal outgrowth has been implicated in the pathophysiology of epilepsy (Bausch, 2005; Cavazos and Cross 2006) and pain (Melzack et al. 2001) (Fig. 4).

Moreover, BDNF is directly involved in the development of epilepsy (Binder 2004; Tongiorgi et al. 2006) and neuropathic pain (Boucher and McMahon, 2001; Pezet and McMahon 2006). Ongoing experiments aim at showing that LCM can interfere with these NT-induced processes, thereby potentially attenuating the development and/or progression of epilepsy and/or neuropathic pain. A recent study showing that CRMP-2 is deregulated in human brain samples from treatment-resistant epilepsy patients but not from control patients (Czech et al. 2004) makes this hypothesis even more plausible.

Additional *in vitro* experiments suggest that CRMP-2 is involved in neuronal protection from excitotoxicity and apoptosis. LCM has shown strong neuroprotective and antiapoptotic effects following glutamate-induced excitotoxicity in hippocampal slices. Moreover, neuroprotective effects of LCM were also observed in *in vivo* animal models, for example, following status epilepticus. Bretin et al. (2006) suggested recently that CRMPs, in addition to their role in neuronal morphogenesis, may contribute to neuronal plasticity. In detail,

they demonstrated that CRMP-2 is involved in the downregulation of *N*-methyl-D-aspartate receptor subunit NR2B, a key modulator of pain transmission.

In summary, LCM interacts with CRMP-2, and further characterization of the interaction with CRMP-2 will determine whether this interaction leads to symptomatic and/or disease-modifying effects.

Effects in Animal Models of Epilepsy

In a gross screening using the Frings audiogenic seizures (AGS)–susceptible mouse model of anticonvulsant activity, LCM provided protection against sound-induced seizures in mice with an ED_{50} of 0.63 mg/kg, i.p.

In addition, LCM was analyzed in the maximal electroshock (MES) test, which detects inhibition of seizure spread in generalized tonic–clonic seizures (GTCSs) (Borowicz et al. 1997; Swinyard et al. 1952). Convulsions were envoked in mice by electric currents delivered via corneal electrodes. LCM protected both mice ($ED_{50} = 4.5$ mg/kg, i.p.) and rats ($ED_{50} = 3.9$ mg/kg, p.o.) against tonic-extension seizures induced by MES, indicating that LCM is effective in preventing seizure spread. In the 6-Hz psychomotor seizure test, which is regarded as a model for treatment-resistant seizures, LCM showed full efficacy with an ED_{50} of 9.99 mg/kg. In contrast, other drugs acting at the voltage-gated sodium channel, for example, LTG, PHT, and CBZ, exhibited partial efficacy only at doses that produce behavioral toxicity (Barton et al. 2001). In the 6-Hz model, LCM exhibited additive to synergistic effects with a variety of AEDs (pronounced synergism observed with levetiracetam and CBZ).

LCM was tested in different models of chemoconvulsant-induced seizures. It did not block GTCSs induced by the $GABA_A$-receptor antagonist bicuculline or the chloride channel blocker picrotoxin. LCM was also ineffective against clonic seizures induced by the subcutaneous bolus injection of the chemoconvulsant pentylenetetrazole in rats and mice. However, LCM given to mice significantly increased the threshold for minimal seizures induced by the more-discriminating timed i.v. infusion of metrazole (Löscher 1999; Stohr et al. submitted).

In addition, LCM was analyzed in the kindling model, which provides a tool to predict activity against complex partial seizures. The calculated ED_{50} of LCM for reduction of the seizure score from 5 to ≤ 3 in fully kindled rats was 13.5 mg/kg (Fig. 5).

Furthermore, activity of LCM (25 mg/kg) was also compared with that of reference AEDs administered at maximally effective doses (PHT 150 mg/kg, CBZ 50 mg/kg, valproic acid 250 mg/kg, and ethosuximide 250 mg/kg) in hippocampal-kindled rats. LCM was superior, in this model, to any of the other drugs in decreasing after-discharge duration by $>85\%$.

The kindling model was also used to evaluate whether LCM affects kindling-induced epileptogenesis. The rats were treated with either vehicle or different doses of LCM (3, 10, or 30 mg/kg/day) over 22–23 days during amygdala kindling. Daily administration of LCM during kindling acquisition produced a dose-dependent effect on kindling development. Although the drug was inactive at 3 mg/kg/day, significant retardation of kindling was observed at 10 mg/kg/day, at which the average number of stimulations to reach kindling criteria was increased by $>90\%$. These data demonstrate that LCM, in addition to exerting anticonvulsant activity, has the potential to retard kindling-induced epileptogenesis (Brandt et al. 2006).

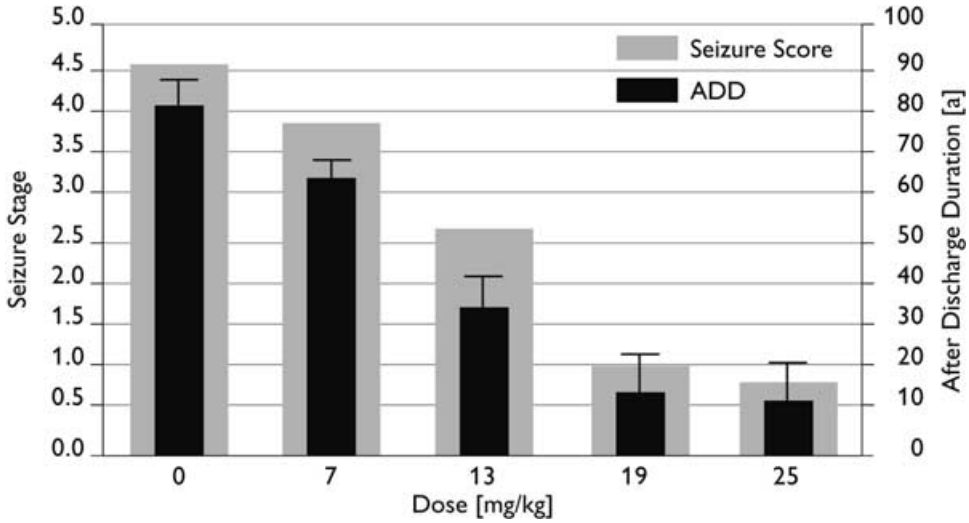

FIG. 5. Lacosamide displays anticonvulsant activity in hippocampal-kindled rats. Male rats were implanted with a bipolar electrode into the ventral hippocampus. After recovery, animals were kindled to a stage 5 behavioral seizure using a stimulus of 50 Hz, 10-sec train of 1-msec biphasic 200 μA pulses delivered every 30 min for 6 h on alternating days for a total of 60 stimulations. Drug testing was initiated after a 1-week stimulus-free period. Fifteen minutes after drug administration each rat was stimulated every 30 min for 3–4 h with suprathreshold stimulations. After each stimulation individual seizure scores and afterdischarge duration (ADD) were noted. Lacosamide dose dependently reduced ADDs with an ED_{50} of 13.5 mg/kg.

LCM was also active in models of status epilepticus. Limbic seizures induced by self-sustaining status epilepticus (SSSE) in rats stopped within 15 min after LCM injection and did not recur over the next 24 h. Spike frequency significantly decreased and only separate spikes were recorded for 12 h after induction of SSSE. In the control group, 3 of the 6 animals died, whereas, in the treatment group, all survived. Histological examination of brain sections (dorsal hippocampus) collected 72 h after status epilepticus revealed significantly less damage in LCM-treated rats compared with control animals, suggesting LCM may be neuroprotective.

Table 3 provides the anticonvulsant profile of LCM in several seizure models in comparison with clinically available AEDs. In summary, LCM has a unique profile in models for epilepsy with efficacy in the dose range 1–30 mg/kg, i.p. This dose range corresponds well with respect to plasma levels when compared to the clinically tested doses of LCM, that is, 200 mg, 400 mg, and 600 mg b.i.d.

Effects in Animal Models of Pain

LCM demonstrated antinociceptive potential in experimental animal models that reflect distinct types and symptoms of pain.

LCM was tested in the mouse and rat tail-flick test (D'Amour and Smith 1941; Ness and Gebhart 1986), a standard primary acute pain screening test, designed to assess the effects of test substances on a centrally mediated reflex response to a noxious thermal stimulus and showed no effect up to a dose of 40 mg/kg (Morrow et al. 2001).

TABLE 3. Anticonvulsant profile of lacosamide in several seizure models in comparison with clinically available AEDs.

Test Substance	MES	s.c. Met	i.v. Met	s. c. Bic	s. c. Pic	NMDA	AGS	Kindling Acq	Kindling Expr	Absence	Status epilepticus
Phenytoin	+	0	0	0	0	0	+	0	±	0	±
Carbamazepine	+	0	0	0	±	0	+	0	±	0	±
Valproic acid	+	+	+	±	±	0	+	n.t.	±	+	±
Felbamate	+	+	n.t.	0	+	+	+	n.t.	±	n.t.	+
Gabapentin	+	+	n.t.	0	0	n.t.	+	n.t.	+	0	n.t.
Lamotrigine	+	0	n.t.	0	0	n.t.	+	±	+	+	0
Topiramate	+	0	+	0	0	n.t.	+	±	+	±	0
Vigabatrin	0	0	n.t.	+	+	n.t.	±	+	+	−	+
Tiagabine	±	+	0	0	n.t.	n.t.	+	+	+	−	+
Levetiracetam	0	0	0	0	0	0	+	+	+	+	+
Zonisamide	+	0	0	0	0	0	n.t.	+	+	n.t.	n.t.
Pregabalin	+	+	n.t.	n.t.	n.t.	n.t.	+	+	n.t.	0	n.t.
Lacosamide	+	0	+	0	0	+	+	+	+	0	+

+ Protection at doses producing no behavioral toxicity; ± Protection at doses producing some behavioral toxicity or activity in some models but not in others; 0 not active (<50% protection at highest dose tested); − proconvulsive effects (in absence models); n.t., not tested;
MES, maximal electroconvulsive shock; Met, metrazole; s.c., subcutaneous; Bic, bicuculline; Pic, picrotoxin; AGS, audiogenic seizures; Acq, acquisition; Exp expression.

LCM was tested in the mouse and rat formalin test in several independent experiments. The formalin test is a model of sustained pain, induced by an intraplantar injection of formalin to the rat hind paw, which induces a biphasic response, divided into an early phase and a second delayed phase (Dubuisson and Dennis 1977; Tjolsen et al. 1992). LCM attenuated the late-phase formalin-induced nociceptive response starting at 8 mg/kg, the lowest dose tested. At the highest dose tested (32 mg/kg) there was full efficacy, which was comparable to the effect of morphine at the dose tested (8 mg/kg, i.p.). Other anticonvulsant drugs like gabapentin (20−100 mg/kg), LTG (15–30 mg/kg), and CBZ (20 mg/kg) have shown activity in the formalin test. PHT, another AED, was without effect up to a dose of 40 mg/kg (Blackburn-Munro et al. 2002). Thus, the ability of LCM to attenuate the late-phase formalin-induced nociceptive response is shared with some, but not all, anticonvulsant drugs.

Inflammation is associated with the development of sensitized pain states, including allodynia and hyperalgesia. In animal models inflammation is normally induced by injection of phlogistic agents into the plantar aspect of the hind paw, for example, carrageenan (Bhalla and Tangri 1970) or complete Freund's Adjuvant (CFA) test (Yamaguchi 2003). In addition to pain testing, the extent of inflammation can be assessed in animal models by measuring the development of paw edema with the use of a plethysmometer. The CFA model is widely used as a screening model for arthritis (Nagakura et al. 2003). LCM (8–40 mg/kg, i.p.) was tested in several independent studies in the carrageenan model for acute inflammatory pain in comparison to indomethacin (10 mg/kg), morphine (8 mg/kg), and aspirin (256 mg/kg) (Stohr et al. 2006). Tactile allodynia, mechanical hyperalgesia, thermal

hyperalgesia, and edema were analyzed. LCM dose-dependently reversed mechanical hyperalgesia starting at 10 mg/kg, and reduced tactile allodynia at 16 mg/kg and thermal hyperalgesia at 32 mg/kg. It had no effect on edema. Morphine had no effect on edema but inhibited tactile allodynia and thermal hyperalgesia. Indomethacin had a comparable effect to LCM on mechanical hyperalgesia. Aspirin had no effect on thermal hyperalgesia but attenuated tactile allodynia and reduced paw edema. Overall, LCM reduces inflammatory pain behavior but has no effect on acute inflammation. Comparing the results in literature, LCM seems to be similarly potent in the carrageenan model for acute inflammatory pain as compared to gabapentin and pregabalin. (Field et al. 1997; Hurley et al. 2002; Villetti et al. 2003).

LCM (20, 30, and 40 mg/kg, i.p.) was investigated in the rat CFA arthritis model using the modified Randall–Selitto test to assess mechanical hyperalgesia (Stohr et al. 2006). Pain behavior was analyzed in rats 11 days post-CFA injection. LCM showed dose-dependent antinociceptive effects. The antinociceptive effects started at a dose of 30 mg/kg and were most prominent during the first 60 min of testing. Morphine (10 mg/kg, i.p.), as a positive control substance, had clear antinociceptive effects in arthritic and normal animals. Under this chronic inflammatory pain condition LCM had full intrinsic antinociceptive activity. In contrast, gabapentin and CBZ were not active against CFA-induced mechanical hyperalgesia (Nagakura et al. 2003; Patel et al. 2001).

The injection of the metabolic inhibitor, monosodium iodoacetate, into the knee joint is a frequently used rat model for analyzing effects of drugs on the pathology of osteoarthritis and characterizing their effects on pain behavior. LCM (3, 10, and 30 mg/kg) was able to reduce secondary mechanical allodynia and hyperalgesia comparable to morphine (3 mg/kg). In contrast, diclofenac (30 mg/kg) was effective in reducing only secondary mechanical hyperalgesia. In this model, pain is induced mainly by inflammation during the first week, whereas afterward inflammation plays only a minor role. LCM was able to inhibit pain behavior during the inflammatory and the noninflammatory phases of arthritis development. This shows that LCM is able to reduce pain behavior induced by multiple mechanisms in animals.

In summary, LCM displayed antihyperalgesic effects in different models for acute and chronic inflammatory pain with similar or even higher potency and efficacy as compared to other anticonvulsant drugs. The effectiveness of LCM in these models suggests that it might have clinically relevant effects in patients suffering from pain conditions such as arthritis.

Furthermore, LCM was tested in the streptozotocin rat model of diabetic neuropathic pain in comparison to drugs that are commonly used in the treatment of diabetic neuropathic pain, that is, antidepressants and anticonvulsants (Beyreuther et al. 2006). Diabetes was induced by intravenous injections of streptozotocin in the left saphena magna. Blood glucose levels were checked before each phase of behavioral testing. Tests for allodynia (cold bath at 4°C and warm plate at 38°C) were performed on day 10 after the induction of diabetes with streptozotocin and tests for hyperalgesia (paw pressure and hot plate at 52°C) and dynamic mechanical allodynia (brushing test) were performed on day 21. As expected, LCM had no acute antinociceptive effects in nondiabetic animals indicating specific antihyperalgesic and antiallodynic effects under conditions of diabetic neuropathic pain. In diabetic rats, LCM attenuated cold (10, 30 mg/kg, i.p.), warm (3, 10, 30 mg/kg, i.p.), and mechanical allodynia (30 mg/kg, i.p.). Streptozotocin-induced thermal and mechanical hyperalgesia were reduced by LCM at doses of 10 and 30 mg/kg, i.p. Morphine (3 mg/kg) showed similar efficacy

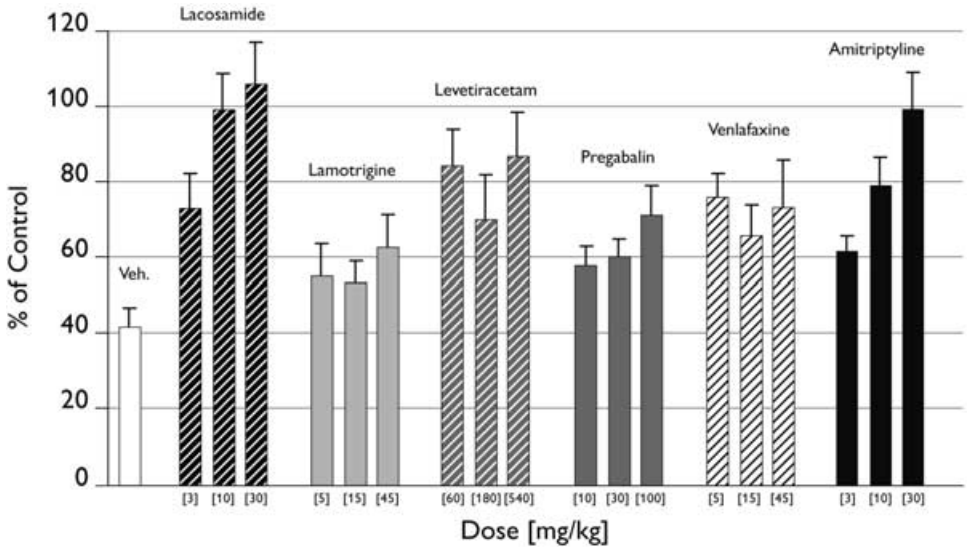

FIG. 6. Lacosamide and amitriptyline reversed thermal allodynia in the STZ model. (Modified from Beyreuther et al. 2006). Diabetic neuropathic pain was induced by acute administration of streptozotocin (55 mg/kg, i.v.) in rats. Animals were placed in a glass cylinder on a warm plate adjusted to 38°C on day 10 after treatment with STZ. The latency of the first reaction (licking, moving the paws, little leaps, or a jump to escape the heat) was recorded with a cut-off time of 30 sec. The activity of different anticonvulsants and antidepressants on allodynia and hyperalgesia was investigated starting 30–45 min after drug treatment and expressed as percentage of pain threshold of nondiabetic control rats.

on allodynia and hyperalgesia. Amitriptyline (10 mg/kg), venlafaxine (15 mg/kg), levetiracetam (180 mg/kg), and pregabalin (100 mg/kg) exhibited significant effects on thermal allodynia and mechanical hyperalgesia. Only treatment with amitriptyline (30 mg/kg, i.p.) produced full reversal of thermal allodynia comparable to LCM. LTG (45 mg/kg, i.p.) had no effect on both behavioral readouts (Figs. 6 and 7). Overall, LCM exhibited potent and broad-spectrum antinociceptive efficacy on neuropathic pain–like behaviors in an animal model for painful diabetic neuropathy.

In addition, LCM was evaluated in animal models for central neuropathic pain, that is, the infra-orbital nerve and the spinal cord injury model (Hao et al. 2006). In rats with infraorbital nerve injury, LCM reduced mechanical hypersensitivity and the effect was markedly stronger in female than in male rats. In spinal cord injured female rats 10–20 mg/kg LCM dose-dependently alleviated the mechanical and cold allodynia-like behaviors without causing motor impairments or marked sedation. At 20 mg/kg, twice daily for 7 days, LCM totally alleviated the allodynia-like state in spinally injured rats with no tolerance. Following treatment cessation the cold and the static allodynia reappeared, but the effect on dynamic mechanical allodynia (brushing) was maintained until day 11.

To assess the local anesthetic effect of LCM an animal model described by Regnier (1929) was used. The effect was assessed in conscious rabbits by measuring the threshold necessary to induce a corneal reflex after rapid touching of the cornea with filaments. The lower concentration of LCM (0.5%) was only marginally active. At the highest concentration (2%), LCM produced a significant effect, slightly greater than that observed with lidocaine

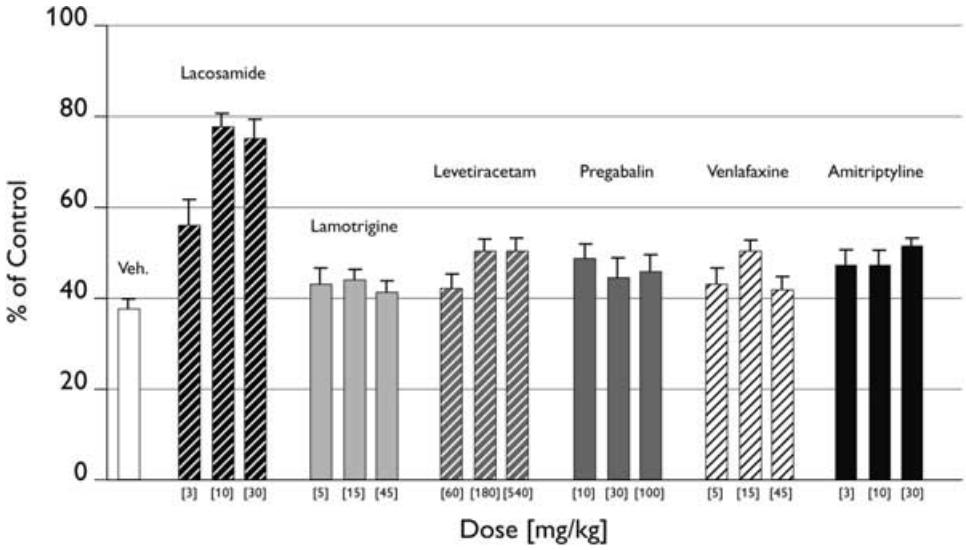

FIG. 7. Lacosamide and amitriptyline reversed mechanical hyperalgesia in the STZ model. (Modified from Beyreuther et al. 2006). Diabetic neuropathic pain was induced by acute administration of streptozotocin (55 mg/kg, i.v.) in rats. The nociceptive flexion reflex was quantified using the Randall–Selitto paw pressure device (Bioseb, France), which applies a linearly increasing mechanical force to the dorsum of the rat's hind paw at day 21 after treatment with STZ. The mechanical nociceptive threshold was defined as the force in grams at which the rat withdrew its paw. The cut-off pressure was set to 250 g. The activity of different anticonvulsants and antidepressants on allodynia and hyperalgesia was investigated starting 30–45 min after drug treatment and expressed as a percentage of pain threshold of nondiabetic control rats.

at 0.5%, but smaller than that with lidocaine at 2%. The results indicated that LCM exerts a moderate dose-dependent local anesthetic effect at high concentrations.

In summary, LCM has broad analgesic activity in multiple animal models for chronic pain (Table 4). The effects were mostly observed at doses ranging from 3 to 30 mg/kg, i.p., which with respect to drug exposure correspond to the clinically tested doses of 200 mg, 400 mg, and 600 mg b.i.d.

TABLE 4. Summary of lacosamide's effects on pain behavior in animal models.

	Tail-flick	Formalin	Carrageenan	CFA	STZ	MIA	SCI	ION
Thermal allodynia	n.t.	n.t.	n.t.	n.t.	+	n.t.	+	n.t.
Mechanical allodynia	n.t.	n.t.	+	n.t.	+	+	+	+
Thermal hyperalgesia	n.t.	n.t.	+	n.t.	+	n.t.	+	n.t.
Mechanical hyperalgesia	n.t.	n.t.	+	+	+	+	+	n.t.
Others pain endpoints	0	+	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
Edema	n.t.	n.t.	0	n.t.	n.t.	n.t.	n.t.	n.t.

n.t., not tested; + activity, 0 no activity.

CFA, complete Freund's adjuvant test; STZ, streptocotozin-induced diabetic neuropathic pain; MIA, monosodium iodoacetate–induced arthritic pain; SCI, spinal cord injury–induced pain; ION, infraorbital nerve injury–induced pain.

Safety Pharmacology

In accordance with the International Conference on Harmonization, Food and Drug Administration (ICH) S7A and S7B guidelines, safety pharmacology studies have been conducted on the central nervous, cardiovascular, and respiratory systems as well as the autonomic nervous, renal, and gastrointestinal systems. The predominant route of administration in the animal studies was oral, which is the main intended clinical route of administration of LCM.

Effects on the central nervous system

LCM has been assessed for its effects on the central nervous system in mice and rats. In several studies dose-dependent behavior-depressant effects have been observed. These manifested as sedation, reduced spontaneous locomotor activity, and impairment of motor coordination. The effects start at doses that are in the upper range of those effective in different pain and epilepsy models in mice and rats. Such effects are commonly seen after treatment with anticonvulsant drugs with different modes of action (Hönack and Löscher 1995; Luszczki et al. 2005). Safety indexes (oral doses producing minimal motor impairment divided by the ED_{50} for the MES test in rats) were calculated using the National Institutes of Health (NIH) anticonvulsant drug screening program for several anticonvulsant drugs. The safety index for LCM was 128-fold, and thus comparable or higher than that of other drugs such as valproate (2-fold), PHT (22-fold), LTG (101-fold), gabapentin (6-fold), or CBZ (101-fold). More severe central nervous side effects, that is, ataxia, tremor, and seizures, were visible at doses of LCM, which are about 2- to 3-fold higher as compared to doses that cause sedation and reduced locomotor activity. The paradoxical effect of increased seizure activity after treatment with anticonvulsant drugs can occur with AEDs of any mechanism of action (Sazgar and Bourgeois 2005).

Effects on cardiovascular and autonomic nervous systems

To assess the action of LCM on the cardiovascular and the autonomic nervous system several cardiovascular *in vitro* and *in vivo* studies were conducted. At concentrations in the upper range of therapeutic plasma levels LCM produced a statistically significant reduction of action potential duration (APD) and a tendency to reduce the maximal upstroke velocity (V_{max}) in the isolated canine Purkinje fiber. Similar effects have been reported for other anticonvulsant compounds that target the sodium channel, for example, PHT, CBZ, or LTG (Mestre et al. 2000).

In order to elucidate the mechanism causing the effect of LCM in Purkinje fibers, the action of this compound on several cardiac ion currents was determined. In recombinant systems the effect of LCM on the potassium current mediated by the human hERG channel was studied. Inhibition of this channel has been associated with fatal arrhythmias. LCM only minimally affected hERG current at concentrations as high as 3000 μmol/L. An overview of AED effects on the hERG channel is given in Table 5 (according to Danielsson et al. 2003, 2005b).

For some of these drugs the ratio of *in vitro* IC_{50} for hERG versus the therapeutic free plasma concentration is close to 30 or lower, which indicates a potential for Q-T prolongation and proarrhythmia (Webster et al. 2002). LCM seems to be devoid of this risk.

TABLE 5. AED effects on the hERG channel.

Compound	PHT	PB	CBZ	LTG	TPM	GP	LCM
Therapeutic plasma level [μmol/L]l	4–10	20–100	5–12	5–30	13–50	70–120	10–60
IC_{50} hERG [μmol/L]	242	~3000	—	223	—	—	7% inhib. at 3 mM
IC_{20} hERG [μmol/L]	—	—	205	—	87	54	—

PHT, phenytoin; PB, phenobarbital; CBZ, carbamazepine; LTG, lamotrigine; TPM, topiramate; GP, gabapentin; LCM, lacosamide; —, IC_{50} not tested.

The L-type Ca^{2+} current, as assessed in human atrial and guinea pig ventricular myocytes, was not affected by LCM concentrations corresponding to about 100-fold the therapeutic plasma concentration.

In contrast, Na^+ current in human atrial myocytes and mammalian cells expressing the human cardiac SCN5A channel was inhibited dose-dependently by LCM. At concentrations in the upper therapeutic range, inhibition of sodium current mediated by recombinant Na^+ channels amounted to about 10–20%. Inhibition was incomplete in recombinant Na^+ channels, leveling off at about 70% at concentrations 20-fold higher than therapeutic plasma levels. In these test systems a positive use dependence of inhibition was observed. In human atrial myocytes no effect of LCM was seen at a hyperpolarized membrane potential. However, at the more depolarized membrane potential of −70 mV LCM induced a pronounced concentration-dependent decrease of Na^+ current. The higher inhibitory potency at more depolarized membrane potentials and positive use dependence in recombinant sodium channels suggest that LCM interacts with an inactivated conformation of the cardiac sodium channel, which would be in line with its activity on neuronal Na^+ channels. Slow inactivation of cardiac sodium channels is less pronounced as compared to skeletal sodium channels, which are similar to neuronal sodium channels. The incomplete inhibition of recombinant cardiac sodium channels by LCM indicates that it selectively enhances slow inactivation in cardiac sodium channels as well. However, the effect of LCM on the slow inactivation of cardiac sodium channels has not been tested. Nevertheless, it seems most likely that LCM's mode of action is the same in neuronal and cardiac sodium channels.

The investigations on cardiac ion currents suggest that inhibition of sodium currents is responsible for the changes in action potential shape in Purkinje fibers.

Studies in anesthetized dogs showed that LCM induced short-lasting hypotensive effects, which appeared at the time of maximal drug plasma levels after i.v. application. The LCM plasma levels eliciting this effect were in the upper range of plasma levels found in humans after receiving the highest recommended dose. The reduction of blood pressure is most likely due to a cardiodepressant action and not an effect on blood vessels, because no change in peripheral resistance was observed. The cardiodepressant activity was characterized mainly by reduced contractility as indicated by decreases in systolic left ventricular pressure (LVP), velocity of pressure change (dP/dt), and reduced cardiac output. These changes were dose dependent and accompanied by a transient increase in PR interval and QRS complex duration.

The negative inotropic and dromotropic effects of LCM are caused most likely by its action on the cardiac sodium channel. Similar effects have been described by Honerjäger and coworkers for a number of different Na^+-current inhibiting compounds in guinea pig

papillary muscle *in vitro* (Honerjäger 1986; Honerjäger et al. 1986). It should be mentioned that in repeated-dose toxicology studies in dogs no gross changes in the ECG were reported. This might be due to the transient nature of these effects or a better tolerability of LCM in awake animals.

The influence of LCM on the autonomic nervous system was assessed by measuring the blood pressure response of anesthetized dogs to several autonomic agonists. The results suggest that LCM does not exhibit major interference with the autonomic control of blood pressure. *In vitro* experiments with autonomic agonists on the isolated ileum did not show any interference either.

Respiratory system

The respiratory function was assessed by whole body plethysmography in Wistar rats. LCM did not show any influence at doses, which yield plasma levels exceeding therapeutic levels in humans.

Effects on renal and gastrointestinal systems

Possible effects of LCM on renal and gastrointestinal function were assessed in rats. LCM did not show an effect on urine volume, saluresis, and kaliuresis, but moderately reduced the velocity of gastrointestinal transit, reaching a maximal effect of about 30% reduction.

Abuse liability

Although neither its pharmacological properties nor its mode of action is known to be associated with a risk for abuse liability, LCM was assessed in a number of preclinical studies for potential abuse liability, since it is centrally acting via a novel mechanism of action.

LCM and its major desmethyl metabolite did not bind with significant affinity to any of 20 abuse- and dependence-related targets used. In addition, LCM did not show reinforcing effects in the conditioned place preference test in rats. Reevaluation of chronic toxicity studies in rats and dogs showed no signs of tachyphylaxis with prolonged administration of LCM and also no syndromes of behavioral and/or physical dependence on withdrawal.

In summary, LCM showed a safety pharmacology profile, which is better or comparable to that of other AEDs. Delay in cardiac conduction due to inhibition of cardiac sodium current is an adverse effect shared with other anticonvulsant drugs acting on the Na^+ channel, like CBZ or PHT. Cardiovascular side effects were observable in anesthetized dogs, the most sensitive animal species tested, starting at plasma levels, which are similar to those obtained after 600 mg of LCM in the clinic. However, the same plasma levels were measured at the no-observed-adverse-effect level (NOAEL) in awake dogs in a 1-year toxicology study. In this study no ECG abnormalities were detected.

Cytochrome P450 (CYP) interaction potential

LCM showed no potential to induce the activity of CYP isoforms 1A2, 2B6, 2C9, 2C19, and 3A4 in human hepatocytes at therapeutic concentrations. The potential of LCM to

TABLE 6. Effects of lacosamide on cytochrome P450 enzyme activities.

CYP isoform	Result
CYP1A1	IC_{50} 47882 μM
CYP1A2	No inhibition detected
CYP2B6	No inhibition detected
CYP2C8	No inhibition detected
CYP2C9	IC_{50} 10214 μM
CYP2C19	IC_{50} 1797 μM
CYP2D6	No inhibition detected
CYP2E1	No inhibition detected
CYP3A4	IC_{50} 2804 μM
CYP3A5	IC_{50} 3305 μM

Activities of human cytochrome P450 enzymes (CYP) were assayed in the presence of lacosamide or specific control inhibitors. Conversion of each substrate to the corresponding product was determined by fluorimetry (Hansen K, Schneider A, Becker K, Schwarz Biosciences GmbH, data on file).

inhibit CYP isoforms 1A2, 2A2, 2C9, 2C19, 2D6, 2E1, and 3A4 was investigated using human hepatocytes. No inhibition was observed except for CYP2C19 (60% inhibition). In subsequent studies with the recombinant human enzymes CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5 LCM showed no or low inhibitory interactions (Table 6). Given that the inhibitory concentrations are more than 30-fold higher than human LCM plasma levels, the data suggest a low risk for the inhibition of CYP isoforms by LCM *in vivo.*

TOXICOLOGY

A complete preclinical toxicology program has been completed for LCM. This included single- and repeated-dose studies in mice, rats, and dogs for up to 3, 6, and 12 months, respectively. A standard genotoxicity test battery as well as 2-year carcinogenicity studies in mice and rats were performed. Furthermore, LCM was tested in rats and rabbits for effects on fertility, early and embryo-fetal development, and pre-/postnatal development including maternal function. In addition, a study in juvenile rats has been completed. Finally, LCM was tested for local tolerance, sensitization, immunotoxicity, as well as phototoxicity (all data on file at Schwarz Biosciences GmbH, Alfred-Nobel-Str. 10, 40789 Monheim, Germany).

Repeated Dose Toxicity Studies

Overall, the repeated dose toxicity studies have demonstrated that LCM is well tolerated in rats and dogs after either intravenous or oral administration. Similarly, repeated-dose oral administration of LCM to mice was not associated with significant toxicity. The dog was slightly more sensitive to LCM exposure than rodents were. All treatment-related effects observed in rats and dogs were completely reversible within a 4-week recovery period.

Clinical signs observed in the chronic toxicity studies in mice, rats, and dogs were dose dependent and included neurological signs such as ataxia, abdominal and/or lateral position,

reduced motility, tremor, or convulsions at high doses. In most cases, these signs can be attributed to exaggerated pharmacodynamic effects of LCM and were considered dose limiting. Similar CNS-related pharmacodynamic effects were also reported from preclinical studies with other AEDs like pregabalin (ataxia, hypo- and hyperactivity; Pharmacology review, Approval package for Lyrica, FDA homepage). In particular, it is important to note that other major AEDs such as PHT, gabapentin, or CBZ are known to exert proconvulsant activity at high, supra-therapeutic doses (Perucca et al. 1998; Sazgar and Bourgeois, 2005).

Genotoxicity and Carcinogenicity Studies

In genetic toxicity tests, LCM was negative in the *in vitro* Ames test, *in vivo* mouse micronucleus test, and *in vivo* rat unscheduled DNA synthesis (UDS) test. Though a weak effect was observed *in vitro* in the mouse lymphoma assay, its biological relevance *in vivo* is unknown. Since no genotoxic properties were observed *in vivo* in two species (mouse and rat) in two different organs (bone marrow and liver) using two endpoints (chromosomal aberration and primary DNA damage), and since LCM possessed no neoplastic properties in the 2-year carcinogenicity studies in mice and rats, tested up to a maximum-tolerated dose, the clastogenic effect observed *in vitro* is not considered biologically relevant *in vivo.* For comparison, other drugs approved for treatment of epilepsy and/or neuropathic pain were reported to cause tumors in animals *in vivo* with unknown relevance to humans; for example, pregabalin-induced hemangiosarcoma in mice (SPC Lyrica® Pfizer Ltd, Kent, UK) and hepatocellular adenomas and carcinomas were reported for duloxetine (SPC Xeristar® Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany).

Reproduction and Developmental Toxicity Studies

LCM was also tested for effects on all stages of reproduction, that is, on fertility, early and embryo-fetal development, and pre-/postnatal development including maternal function, by oral administration to rats or rabbits. Developmental toxicity was observed at a maternally toxic dose, but there was no evidence of adverse effects on male or female reproductive function or teratogenicity. The lack of evidence for teratogenic effects in animals is promising as for many other frequently used AEDs; for example, PHT (SPC Phenytoin® Antigen Pharmaceuticals Ltd, Roscrea Co. Tipperay), valproate (SPC Orlept® Desitan Arzneinittel GmbH, Hamburg, Germany), or zonisamide (SPC Zonegram® Eisai Ltd, London, UK), malformations and abnormalities have been reported in animals and/or in the clinical use. In particular, the control of status epilepticus during pregnancy is imperative due to its inherent adverse effects on the fetus, specifically hypoxia.

Studies in Juvenile Animals

In a juvenile toxicity study in rats, in principle, the same effects as in adult animals were noted. However, the juvenile animals appeared to be less affected than adults by LCM treatment. Body weight reduction was dose limiting and, as a secondary effect to this, a slightly delayed development in the high-dose groups in general, was observed. All findings were completely reversible within a 4-week treatment-free recovery period; however, body weight in high-dose animals was still slightly reduced. No test substance-related effects

were noted on auditory function, learning, and memory in the Morris water maze test, grip strength, locomotor activity, observational neurological screening, or at macroscopic or histomorphological examination. A slight anxiolytic-like effect was noted in the open-field test in the intermediate and high-dose groups indicated by a significantly decreased latency time to first movements. All other parameters were not affected.

Overall, no treatment-related adverse effects were noted on the developing rat brain either on the histomorphological or functional level, that is, there was no evidence of specific CNS-developmental impairment. This is important to note as several other AEDs, for example, sulthiame, valproate, PHT, phenobarbital, diazepam, clonazepam, and vigabatrin, have been reported to cause widespread and dose-dependent apoptotic neurodegeneration in the developing rat brain (Bittigau et al. 2002, 2003; Glier et al. 2004; Manthey et al. 2005). In contrast, LCM showed neuroprotective and antiapoptotic effects *in vitro.*

Other Toxicity Studies

LCM showed good local tolerability, no hemolytic properties or skin-irritating properties in rabbits, and no sensitizing properties in guinea pigs. In addition, there was no sign of immunotoxicity in the repeated-dose toxicity studies or in a plaque-forming colony assay in mice. LCM is not expected to possess any direct photosensitizing properties. However, LCM was classified as being irritating to the eyes.

CONCLUSIONS

LCM has a novel dual mechanism of action, that is, selective enhancement of sodium channel slow inactivation and modulation of CRMP-2 activity. The drug demonstrated antiepileptic effectiveness in different rodent seizure models for generalized and complex partial seizures as well as for status epilepticus.

The results of animal pain studies suggest that LCM may have specific antihyperalgesic activity under conditions of chronic neuropathic and inflammatory pain, which is not due to the local anesthetic effects. For this reason LCM is under evaluation for osteoarthritis, cancer pain, central pain, and fibromyalgia. The broad preclinical analgesic and anticonvulsant profile of LCM may be due to the unique dual mode of action underlying its activity.

The safety pharmacological effects seen for LCM, that is, a mild behavioral-depressant activity and slowing of cardiac conduction, have also been described for other AEDs. They are dose dependent and fully reversible. The current preclinical data on LCM do not indicate any potential for abuse liability. LCM had a minimal interaction with the cytochrome P450 (CYP) system *in vitro* and thus is predicted to have a low potential for pharmacokinetic interaction with concomitant drugs, which are substrates of CYP isoforms. The comprehensive preclinical toxicology program demonstrated that LCM is well tolerated. Most of the observed treatment-related effects, especially the exaggerated pharmacodynamic effects on the CNS, are known from other drugs used in the treatment of epilepsy or neuropathic pain. In contrast to many frequently used drugs, especially those used in treatment of epilepsy, LCM showed a favorable profile in reproductive and developmental animal studies.

LCM's promising preclinical profile differs from that of other anticonvulsants in its mechanism of action, spectrum of activity, pharmacokinetics, and safety profile.

First results of clinical trials in epilepsy show efficacy in highly refractory, partial seizure patients (Ben-Menachem et al. 2005; Biton et al. 2005; Rosenfeld et al. 2005). In patients with diabetic neuropathic pain LCM produced strong and sustained pain reduction with low dropout rates and high patient satisfaction (Hidvégi et al. 2006; McCleane et al. 2003; Shaibani et al. 2006; Wymer et al. 2006). Thus LCM is considered a promising new drug candidate with a broad spectrum of action including epilepsy, diabetic neuropathic pain, and other indications.

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