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Lack of effect of two oral sodium channel antagonists, lamotrigine and 4030W92, on intradermal capsaicin-induced hyperalgesia model

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Abstract

Preclinical studies have emphasized that persistent small afferent input will induce a state of central facilitation, which can be regulated by systemically administered sodium channel blockers. We have extended these preclinical studies to the human volunteers by examining the effects of lamotrigine and 4030W92, two structurally related voltage-sensitive sodium channel antagonists, on acute sensory thresholds and facilitated processing induced by intradermal capsaicin. Fifteen healthy subjects received 4030W92, lamotrigine, and placebo in a randomized order using double-blinded crossover design methodology in three sessions each separated by a 7-day washout period. In each session, baseline neurosensory testing was performed on the volar aspect of the subject's left forearm. Subjects were then dosed with either lamotrigine (300 mg), 4030W92 (100 mg), or placebo, followed 2 h later by capsaicin (100 μg) injected intradermally on the volar aspect of the left forearm. Pain scores, blood pressure, heart rate, and respiratory rate were measured at the time of injection and every 5 min for 15 min. Fifteen minutes after the capsaicin injection, the hyperalgesic area was determined by von Frey hair, stroking, and heat; the flare response was outlined; and neurosensory testing again was performed halfway between the edge of the hyperalgesic area and the capsaicin injection site. While capsaicin significantly decreased the hot pain and VF pain thresholds, oral lamotrigine and 4030W92 failed to alter this response to capsaicin, relative to placebo treatment. Similarly, oral lamotrigine or 4030W92 did not alter the pain scores reported from mechanical pain stimuli at any time postcapsaicin. This study showed a lack of effect of two structurally similar sodium channel antagonists on a human experimental pain model using intradermal capsaicin, which is consistent with other studies on the effects of sodium channel antagonists of capsaicin-induced pain and hyperalgesia. This lack of effect stands in contrast to reported effects of sodium channel antagonists on preclinical models of cutaneous hyperalgesia or effects of lamotrigine on clinical neuropathic pain.

Keywords: Antagonists; Capsaicin; Channel; Experimental; Pain; Sodium

1. Introduction

Based on preclinical studies, the processing of nociceptive information may be characterized in terms of several discrete mechanisms. These mechanisms reflect the following: (1) the processing of acute nociceptive input (i.e., the pain response ceases with removal of the stimulus); (2) facilitated states (windup) that arise from persistent afferent input (as after tissue injury); and (3) altered processing that arises secondary to nerve injury, both yielding states of hyperalgesia and allodynia. Parallel pathological states have been shown to exist in humans, and experimental models believed to reflect the different mechanisms of nociceptive processing have been developed. However, the pharmacology of these experimental models is just beginning to be understood. An important question is whether the effects of a drug on one nociceptive processing mechanism will predict the effect on other mechanisms.

Intradermal capsaicin results in the transient (<20–30 min) and selective activation of C fibers. Such an injection results in a brief pain state that, upon disappearance, is replaced by an enlarged area of tactile allodynia and thermal hyperalgesia that persists for an extended interval (LaMotte et al., 1991). It is thought to represent a facilitated pain state that arises from persistent afferent input. Several lines of evidence developed in preclinical models suggest that both

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spontaneous and evoked pain are mediated in part by voltage-sensitive sodium channels (Cummins and Waxman, 1997; Devor et al., 1993; England et al., 1996). In animals, the systemic delivery of sodium channel antagonists in concentrations that do not block axon conduction will reduce facilitated spinal processing induced by tissue injury (Jett et al., 1997; Kamei et al., 1993; Tanelian and MacIver, 1991). However, the sodium channel blockers lidocaine and mexiletine have yielded mixed results on capsaicin-induced pain and hyperalgesia responses in human studies (Ando et al., 2000; Wallace et al., 1997).

Lamotrigine and 4030W92 are two structurally related voltage-sensitive sodium channel antagonists that have undergone clinical trials in the treatment of nociceptive and neuropathic pain. Lamotrigine titrated to 400 mg/day has been shown to be effective in several well-defined neuropathic pain populations such as trigeminal neuralgia (Zakrzewska et al., 1997), painful diabetic neuropathy (Eisenberg et al., 2001), and chemotoxic AIDS neuropathy (Simpson et al., 2002; Simpson et al., 2000) but found ineffective at doses of 200 mg/day in mixed diagnoses (McCleane, 1999). The effects of lamotrigine have also been studied on acute nociceptive input and facilitated pain in experimental models. Lamotrigine in a single 300-mg dose has been shown to decrease acute pain induced by the cold pressor test but not acute chemically induced nociception (Klamt and Posner, 1999; Webb and Kamali, 1998). A single 200-mg dose of lamotrigine administered presurgically has been shown to significantly reduce the analgesic requirements of postoperative pain (Bonicalzi et al., 1997).

Recently shown to be ineffective in the treatment of neuropathic pain at a daily dose of 25 mg was 4030W92, a more potent analog that produces voltage and use-dependent inhibition of tetrodotoxin (TTX) resistant and sensitive sodium channels (Wallace et al., 2001a). However, there are no studies on the effects of 4030W92 and lamotrigine on human experimental hyperalgesia. This study sought to evaluate the effects of a single oral dose of lamotrigine 300 mg and 4030W92 100 mg on the pain and cutaneous hyperalgesia induced by intradermal capsaicin in healthy volunteers. These doses were considered to provide approximately equipotent plasma drug concentrations based on activity in animal models.

2. Methods

2.1. Patients

The study was approved by the University of California at San Diego Institutional Review Board. Fourteen healthy volunteers (9 women, 5 men) were used in the study. Average age (years) was 30 (range 19–47) and average weight (kg) was 73 (range 59–102). Informed consent was obtained after thorough explanation of the study protocol.

2.2. Clinical methods

A randomized, double-blinded, placebo-controlled crossover design methodology was conducted. Subjects participated in three sessions separated by a 7-day washout period. One session was with lamotrigine, one was with 4030W92, and one was with placebo. Exclusion criteria included patients with peripheral nerve injury or neuropathic pain syndromes, persons currently taking anticonvulsants or antiarrhythmics, or patients with heart, hepatic, or renal insufficiency, allergy or hypersensitivity to sodium channel antagonists, pregnancy, or presence of psychiatric illness that would interfere with the interpretation of results. An electrocardiogram was performed on all patients prior to participation in the study. Baseline blood pressure, heart rate, respiratory rate, and temperature were measured. Baseline neurosensory testing was then performed on the volar aspect of the subject's left forearm half-way between the wrist and antecubital fossa (see Section 2.3.1). Subjects were then dosed with either lamotrigine 300 mg, 4030W92 100 mg, or placebo. Two hours postdose, drug side effects were measured and capsaicin (8-methyl *N*-vanillyl 6-nonamide) 100 μg/10 μl of l of a 20% cyclodextran vehicle was injected intradermally on the volar aspect of the forearm. Pain scores, blood pressure, heart rate, and respiratory rate were measured at the time of injection and every 5 min for 15 min. Fifteen minutes after the capsaicin injection, the hyperalgesic area was determined to von Frey hair, stroking, and heat; the flare response was outlined; and neurosensory testing was performed halfway between the edge of the hyperalgesic area and the capsaicin injection site.

2.3. Testing

2.3.1. Neurosensory testing

Three neurosensory tests were performed: (i) warm and cool sensation; (ii) hot and cold pain; and (iii) touch. These tests were performed on the volar aspect of the left forearm. The same order of the stimuli was used in all subjects: touch, cool, warm, cold pain, and hot pain. This order was chosen because it goes from the lowest stimulus (touch) to the highest stimulus (hot pain).

Warm and cool sensations were measured using a Thermal Sensory Analyzer (Medoc Advanced Medical Systems, Minneapolis). This device consists of a thermode measuring 46 × 29 mm. The temperature of the thermode can either rise or fall (at a rate of 1.0 °C/s) depending on the direction of current flow through the device. The subject holds a switch that is pressed at the first sensation of warmth or cold; pressing the switch reverses the temperature change, returning to a neutral temperature of 32 °C.

Warm and cold pain measurements also use the Thermal Sensory Analyzer but the endpoint is pain instead of temperature change sensation. It uses a temperature change rate of 1.5 °C/s.

Touch threshold was measured using von Frey hairs. Calibrated von Frey hairs are filaments of varying size. The filaments are selected at random and three successive stimuli are applied for 2 s at 5-s intervals per filament applied in an ascending pattern. The subject is instructed to report if the stimulus is felt. Thresholds are expressed in milli-Newton and measured as positive if the patient felt any one of the three successive stimuli. At the stimulus intensity evoking a report of discomfort, the next stimulus is one unit lower. This stimulus reversal is repeated twice and the average reversal intensity defined as the threshold. This method is a modification of the widely used method of Dixon in animal and human psychophysical testing (see, for example, Wallace et al., 1997).

2.3.2. Capsaicin-induced pain and hyperalgesia

At 0, 5, 10, and 15 min postcapsaicin injection, spontaneous pain scores and evoked pain scores to von Frey hair, stroking, and heat (40 °C) were measured using a visual analog scale. At 15 min postinjection, secondary hyperalgesia and flare response were measured. Secondary hyperalgesia was evaluated with a 5.18 von Frey hair (touch), foam brush gently stroked on the skin (stroking), and a 2 × 2-cm probe heated to 40 °C (heat). These stimuli started away from the injection site in a nonpainful area and moved progressively closer in radius until the subject reported pain or tenderness. That site was marked on the skin and a total of eight determinations of the borders of secondary hyperalgesia were outlined on the skin. The area of secondary hyperalgesia and flare response was outlined onto a transparency for area determination (cm^2). The postcapsaicin neurosensory thresholds were tested at a distance halfway between the edge of the area of hyperalgesia and the injection site.

Pain scores were measured using a visual analog scale. The subject places a mark along the line that corresponds with their pain. This line is 100 mm long with "no pain" at 0 mm and the "worst imaginable pain" at 100 mm. The distance (in mm) gives the measurement of pain.

Side effects were measured using a visual analog scale. If side effects were present, the subject was asked to identify and rate the most severe side effect by placing a mark along the line that corresponds to the severity of the side effect. This line is 100 mm long with "no side effect" at 0 mm and the "worst imaginable side effect" at 100 mm. The distance (in mm) gives the measurement of the side effect.

2.4. Dose selection

The doses chosen for this study represent the highest single dose exposure considered safe for administration to volunteer subjects consistent with minimizing the risk of side effects and unblinding the study. One-time administrations of 300 mg lamotrigine have been used in several studies previously (Klamt and Posner, 1999; Lamb et al., 1995; Webb and Kamali, 1998). A single 100 mg dose of 4030W92 produces a C_{max} similar to the steady-state concentration achieved by the 25 mg daily dose used in the neuropathic pain study (Wallace et al., 2001a). Furthermore, the doses of lamotrigine and 4030W92 produce expected mean C_{max} plasma concentrations that approximate their relative potency in animal models of pain.

2.5. Data analysis

Utilizing previously acquired data (Wallace et al., 1997), sample size determinations for percentage change in pain scores were performed. Setting type I error rate = 0.05 and the type II error rate = 0.20 (i.e., power = 0.80), a necessary sample size of 12–14 was calculated.

Data are expressed as the mean ± S.D. Data for each neurosensory threshold measure (cool, cold pain, warm, hot pain, VF, and VF pain) were compared using a separate two-factor repeated measure ANOVA for each threshold, with both drug treatment (placebo, lamotrigine, 4030W92) and time of neurosensory assessment (precapsaicin, postcapsaicin) as within-subjects measures. Pain scores (spontaneous, VF, stroking, and VF) following capsaicin treatment were also analyzed by separate two-factor repeated measures ANOVA for each pain score, with drug and time postcapsaicin (0, 5, 10, and 15 min) as within-subjects factors. Finally, allodynic areas postcapsaicin (Flare, VF, and stroke) were analyzed by separate single-factor repeated measures ANOVA for each allodynic area, with drug as the within-subjects factor. As appropriate, follow-up comparisons of individual means consisted of paired t tests, with significance held at a constant level of $P < .05$ through the correction method of Bonferroni.

3. Results

In general, oral lamotrigine and 4030W92 were almost entirely without significant effect upon any thermal, mechanical, or pain threshold (Table 1). There were no significant main effects of drug or Drug × Time (pre- or postcapsaicin) interactions for any of the measured neurosensory thresholds, with the single exception of a main effect of drug on cool threshold ($F = 3.89$, $P < .05$). However, as suggested in Table 1, this appears to be due primarily to a small decrease in threshold under the placebo condition relative to baseline assessment; both the lamotrigine and the 4030W92 values are comparable to the baseline values.

While capsaicin significantly decreased the hot pain and VF pain thresholds as indicated by a significant main effect of time pre- or postcapsaicin ($F = 47.89$, $P < .0001$, and $F = 74.56$, $P < .0001$, respectively), the absence of any main effect of drug or Drug × Time interaction for these measures indicated that lamotrigine and 4030W92 failed to alter this response to capsaicin relative to placebo treatment (see rows 5 and 8 of Table 1).

Table 1
Pre- and postdrug thermal thresholds (°C ± S.D.), mechanical thresholds (von Frey = grams of pressure), and thermal elicited pain score (visual analog scale in mm ± S.D.)

	Baseline	Lamotrigine		4030W92		PLACEBO	
		Postdrug	Postcap	Postdrug	Postcap	Postdrug	Postcap
Thermal thresholds							
Cool	29.4 ± 1.5	29.3 ± 1.5	28.9 ± 1.8	29.3 ± 1.5	29.1 ± 1.3	28.8 ± 1.0	28.2 ± 2.8
Warm	34.7 ± 1.4	35.8 ± 3.2	35.8 ± 1.6	35.7 ± 2.1	36.5 ± 2.3	35.6 ± 2.4	36 ± 1.7
Cold pain	6.4 ± 13.2	3.7 ± 5.3	0.5 ± 1.6	3.0 ± 4.4	3.1 ± 6.8	2.8 ± 5.3	4.2 ± 8.7
Cold pain VAS	23.3 ± 26.2	22.2 ± 25.8	14.8 ± 24	17.4 ± 21.6	14.5 ± 20	18 ± 21.2	15.1 ± 20.3
Hot pain	47.7 ± 2.3	47.6 ± 1.5	42.9 ± 3.1	47.5 ± 2.3	43.5 ± 4	47.8 ± 2.1	44.2 ± 3.7
Hot pain VAS	43.7 ± 28.8	44.3 ± 27.6	44.6 ± 25.3	34 ± 20.2	40.8 ± 21.9	30.5 ± 21.4	40.6 ± 20.7
von Frey							
Threshold	3.4 ± 0.5	3.5 ± 0.4	3.4 ± 0.6	3.7 ± 0.4	3.8 ± 0.4	3.5 ± 0.6	3.6 ± 0.5
Pain	6.2 ± 0.7	6.2 ± 0.6	5 ± 0.5	6.3 ± 0.6	5.0 ± 0.4	6.2 ± 0.7	5.5 ± 0.8

The thermal thresholds are the temperature at which the change was detected (from a starting temperature of 32 °C).

ORAL lamotrigine or 4030W92 had no significant effect on the pain scores reported from mechanical pain stimuli at any time postcapsaicin (from 0 to 15 min) (see Fig. 1). Regardless, neither lamotrigine nor 4030W92 shows any indications of attenuating the hyperalgesia associated with capsaicin treatment.

Intradermal capsaicin produced a secondary hyperalgesia and flare response in all volunteers during the placebo

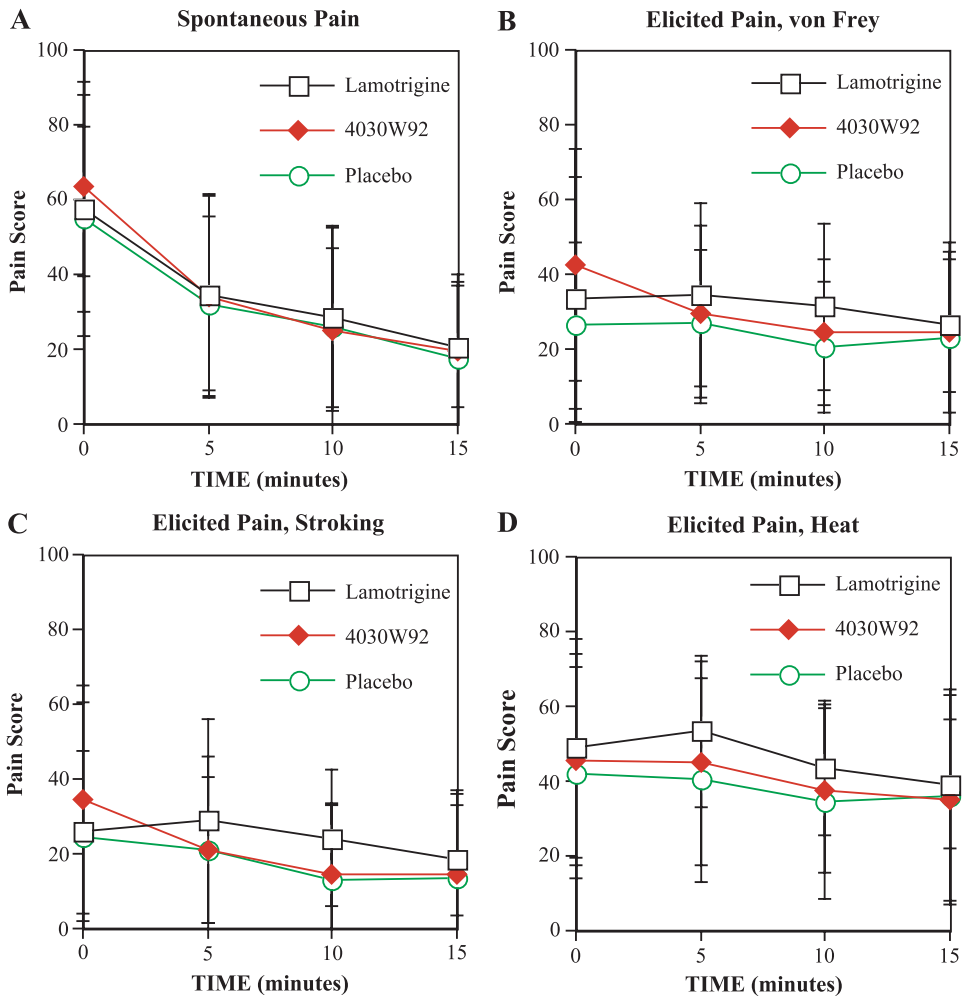

Fig. 1. The effect of oral lamotrigine and 4030W92 on the spontaneous (A) and elicited pain to von Frey hair (Cui et al., 1998), stroking (C), and heat (D) at 0, 5, 10, and 15 min after intradermal capsaicin injection in the volar aspect of the left forearm.

period. After oral lamotrigine and 4030W92, there was no significant reduction in the area of secondary hyperalgesia to von Frey hair or stroking nor was there an effect on the flare response (Fig. 2).

Fifty percent and 71% of the subjects reported side effects from oral lamotrigine and 4030W92, respectively. The most common side effect was dizziness. Fig. 3 shows the mean peak side effect scores. When reported, the range of the side effect score was 12–40 for lamotrigine and 20–75 for 4030W92.

4. Discussion

In a previous study on the effect of 4030W92 on neuropathic pain, there were minimal effects on pain and allodynia (Wallace et al., 2001a), whereas lamotrigine has been shown to be effective in neuropathic pain and acute pain but has never been studied on facilitated pain (Bonicalzi et al., 1997; Webb and Kamali, 1998; Zakrzewska et al., 1997). The purpose of this study was to use a higher acute dose of 4030W92 that was used in the clinical study and a dose of lamotrigine that has been demonstrated to be effective in neuropathic pain and then determine the effects on neurosensory thresholds and facilitated pain. However, we were unable to demonstrate an effect on this experimental model of cutaneous hyperalgesia.

The correlation between sensation and nerve fiber activity has been extensively studied and no firm conclusions can be made. Large myelinated fiber function can be assessed with milli-Newtons of pressure applied to the skin (Gruener and Dyck, 1994); small myelinated fiber function can be assessed with quantitative thermal sensory testing, and small unmyelinated fiber function can be assessed with quantitative thermal sensory testing and mechanical pain (pressure/pinch algometer) (Verdugo and Ochoa, 1992). These basic theories are the premises that established the model used to study the effects of lamotrigine and 4030W92 on neurosensory processing.

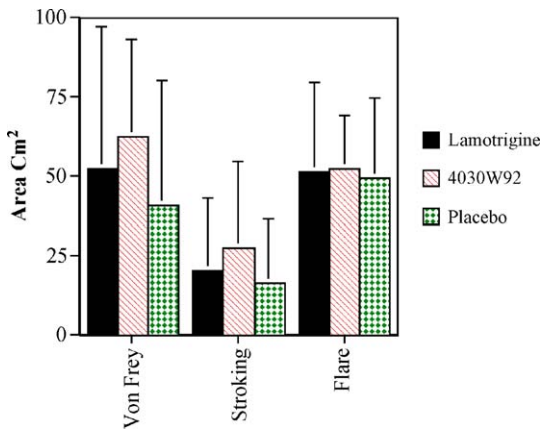

Fig. 2. The effect of oral lamotrigine and 4030W92 on the area of secondary hyperalgesia (cm^2) to von Frey hair, stroking, and the flare response after intradermal capsaicin injection in the volar aspect of the left forearm.

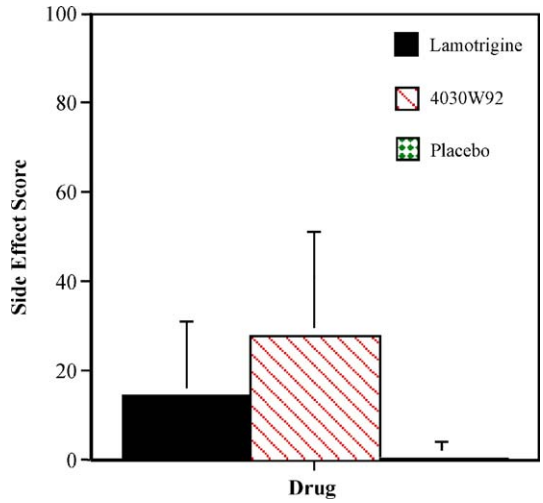

Fig. 3. Peak side effect scores after oral lamotrigine and 4030W92. If side effects were present, subjects were asked to rate them on a scale of 0 (no side effect) to 100 (worst side effect imaginable).

Consistent with previous reports on other sodium channel antagonists, neither lamotrigine nor 4030W92 altered acute sensory thresholds. Studies with intravenous lidocaine and mexiletine in healthy volunteers have shown no effect on acute thermal or mechanical thresholds (both painful and nonpainful) (Ando et al., 2000; Bach et al., 1990; Wallace et al., 1997). This is in contrast to lamotrigine, which has been shown to significantly decrease cold pressor-induced pain scores in healthy volunteers (Lamb et al., 1995; Webb and Kamali, 1998). However, cold pain thresholds are highly variable between subjects, which make it a poor measure of analgesia (Wallace et al., 1997; Wallace et al., 2002).

In animals, the systemic delivery of sodium channel antagonists in concentrations that do not block axon conduction will reduce facilitated spinal processing induced by tissue injury (Jett et al., 1997; Kamei et al., 1993; Tanelian and MacIver, 1991). The central facilitation induced by spinal delivery of a glutamate agonist is blocked by intravenous lidocaine (Biella et al., 1993; Biella and Sotgiu, 1993) and the central release of substance P is inhibited by systemic mexiletine (Kamei et al., 1992), indicating a central action. However, the mg/kg dose administered in these studies is much higher than the maximal tolerable dose in humans, making it difficult to interpret clinically. Although 200 mg lamotrigine administered before surgery has been shown to decrease total analgesic requirements after surgery (Bonicalzi et al., 1997), we failed to demonstrate an effect in this experimental capsaicin model of facilitated pain. This is consistent with other studies that have shown significant effects of intravenous lidocaine on acute postoperative pain but minimal effects on the capsaicin model (Ando et al., 2000; Bartlett and Hutaserani, 1961; Cassuto et al., 1985; Wallace et al., 1997). Although there is an effect of intravenous lidocaine on the flare response and heat

hyperalgesia, there is no effect on secondary hyperalgesia and pain after intradermal capsaicin (Wallace et al., 1997). A recent study by Petersen et al. (2003) failed to show an effect of lamotrigine (400 mg) on pain and hyperalgesia following heat/capsaicin sensitization. These studies suggest that animal models of facilitated processing may correlate better with clinical pain states than with human intradermal capsaicin models of facilitated pain.

Acute pain (i.e., thermal and mechanical) results in a brief report of pain that quickly resolves when the stimulus is removed. This model has been subjected to rigorous pharmacological testing (Ando et al., 2000; Wallace et al., 2003; Wallace and Grubbs, 2002; Wallace et al., 1997; Wallace et al., 2001b). Acute pain is sensitive to the opioids and resistant to most nonopioids. The intradermal injection of capsaicin results in a brief report of intense pain followed by a longer lasting area of secondary hyperalgesia. Like acute pain, this model has been subjected to rigorous pharmacological testing; therefore, much is known about the pharmacology (Ando et al., 2000; Wallace et al., 2003; Wallace and Grubbs, 2002; Wallace et al., 1997; Wallace et al., 2001b). Like acute pain, it is sensitive to the opioids and NMDA antagonists but resistant to most nonopioids (tricyclic antidepressant, mexiletine). The capsaicin/heat hypersensitivity model, a recently described human experimental pain model, uses a minimally painful stimulus that results in a secondary hyperalgesia that can be rekindled with heat application. The pharmacology is less described as compared to the intradermal capsaicin; however, it is known that the model is sensitive to an opioid and gabapentin (Petersen et al., 2001, 2003) and resistant to lamotrigine. Although there appears to be some differences in the pharmacology of these two models, it is difficult to make conclusions on which, if any, of the models are more predictive of analgesic efficacy in clinical pain states.

After intradermal capsaicin, the flare response represents antidromic invasion of the axon collaterals and the subsequent release of neuropeptide (Levine et al., 1993). The blockade of the flare response by sodium channel antagonists has shown mixed results. Previous reports using intravenous lidocaine showed a significant decrease in both the area of flare response and heat hyperalgesia (Wallace et al., 1997) and may reflect a role played by voltage-sensitive sodium channels at the terminals of unmyelinated axons (Hua et al., 1995). In this study, neither lamotrigine nor 4030W92 had a significant effect on the flare response. This is consistent with other studies on oral sodium channel antagonists (Ando et al., 2000).

It is possible that this negative study resulted from the lack of sensitivity of this model to detect analgesia of the agents studied. The model has a significant variability in pain response between individuals that will affect sensitivity (Liu et al., 1998). A positive control shown to be effective in this model (an opioid) was not used; however, previous studies using a positive control that lacks efficacy against a study drug that demonstrates efficacy show that this model can detect differences in these agents (Wallace et al., 2001b). It is unlikely that subtherapeutic levels of lamotrigine and 4030W92 can explain this negative study. Review of the side effects revealed that 50% and 71% of the subjects reported side effects from oral lamotrigine and 4030W92, respectively, which confirms the dose limitations set in this study, likely precluding any further increases in dose. Also, if one assumes that side effects peak with peak plasma levels, it is unlikely that subtherapeutic levels of lamotrigine and 4030W92 resulted in the negative effect.

In conclusion, this study showed no effect of two structurally similar sodium channel antagonists on capsaicin-induced pain and hyperalgesia in human volunteers, which is consistent with previous studies on the effects of sodium channel antagonists in this model. This observation is in contrast to reported positive effects of sodium channel antagonists on preclinical models of cutaneous hyperalgesia and neuropathic pain.

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References

Ando K, Wallace MS, Schulteis G, Braun J. Neurosensory finding after oral mexiletine in healthy volunteers. Reg Anesth Pain Med 2000;25:468–74.

Bach FW, Jensen TS, Kastrup J, Stigsby B, Dejgard A. The effect of intravenous lidocaine on nociceptive processing in diabetic neuropathy. Pain 1990;40:29–34.

Bartlett EE, Hutaserani O. Xylocaine for the relief of postoperative pain. Anesth Analg 1961;40:296–304.

Biella G, Sotgiu ML. Central effects of systemic lidocaine mediated by glycine spinal receptors: an iontophoretic study in the rat spinal cord. Brain Res 1993;603:201–6.

Biella G, Lacerenza M, Marchettini P, Sotgiu ML. Diverse modulation by systemic lidocaine of iontophoretic NMDA and quisqualic acid induced excitations on rat dorsal horn neurons. Neurosci Lett 1993;157:207–10.

Bonicalzi V, Canavero S, Cerutti F, Piazza M, Clemente M, Chio A. Lamotrigine reduces total postoperative analgesic requirement: a randomized double-blind placebo-controlled pilot study. Surgery 1997;122:567–70.

Cassuto J, Wallin G, Hogstrom S, Faxen A, Rimback G. Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. Anesth Analg 1985;64:971–4.

Cui J, Meyerson B, Sollevi A, Linderoth B. Effect of spinal cord stimulation on tactile hypersensitivity in mononeuropathic rats is potentiated by simultaneous GABA(B) and adenosine receptor activation. Neurosci Lett 1998;247:183–6.

Cummins TR, Waxman SG. Down regulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. Neuroscience 1997;17:3503–14.

Devor M, Govrin-Lippmann R, Angelsides K. Na channel immunolocali-

zation in peripheral mammalian axons and changes following nerve injury and neuroma formation. J Neurosci 1993;13:1976–92.
Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay I. Lamotrigine reduces painful diabetic neuropathy. A randomized, controlled study. Neurology 2001;57:505–9.
England JD, Happel LT, Kline DG. Sodium channel accumulation in humans with painful neuromas. Neurology 1996;47:272–6.
Gruener G, Dyck PJ. Quantitative sensory testing: methodology, applications, and future directions. J Clin Neurophysiol 1994;11:568–83.
Hua X-Y, Wong S, Jinno S, Yaksh TL. Pharmacology of calcitonin gene related peptide release from sensory terminals in the rat trachea. Canad J Physiol Pharm 1995;73:999–1006.
Jett M, McGuirk J, Waligora D, Hunter J. The effects of mexiletine, desipramine and fluoxetine in rat models involving central sensitization. Pain 1997;69:161–9.
Kamei J, Hitosugi H, Kawashima N, Aoki T, Ohhashi Y, Kasuya Y. Antinociceptive effect of mexiletine in diabetic mice. Res Commun Chem Pathol Pharmacol 1992;77:245–8.
Kamei J, Hitosugi H, Kasuya Y. Effects of mexiletine on formalin-induced nociceptive responses in mice. Res Commun Chem Pathol Pharmacol 1993;80:153–62.
Klamt JG, Posner J. Effects of lamotrigine on pain-induced chemo-somatosensory evoked potentials. Anaesthesia 1999;54:774–7.
Lamb RJ, Mercer AJ, Posner J. The effect of lamotrigine (300 mg) and dipipanone (4 and 8 mg), alone and in combination, on the cold-pain test in healthy volunteers. Br J Clin Pharmacol 1995;39:565.
LaMotte RH, Shaine CN, Simone DA, Tsai EFP. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J Neurophysiol 1999;66:190–211.
Levine JD, Fields HL, Basbaum AI. Peptides and the primary afferent nociceptor. J Neurosci 1993;13:2273–86.
Liu M, Max MB, Robinovitz E, Gracely RH, Bennett GJ. The human capsaicin model of allodynia and hyperalgesia: sources of variability and methods for reduction. J Pain Symptom Manage 1998;16:10–20.
McCleane G. 200 mg daily of lamotrigine has no analgesic effect in neuropathic pain: a randomized, double-blind, placebo controlled trial. Pain 1999;83:105–7.
Petersen KL, Jones B, Segredo V, Dahl JB, Rowbotham MC. Effect of remifentanil on pain and secondary hyperalgesia associated with the heat-capsaicin sensitization model in healthy volunteers. Anesthesiology 2001;94:15–20.
Petersen KL, Maloney A, Hoke F, Dahl JB, Rowbotham MC. A randomized study of the effect of oral lamotrigine and hydromorphone on pain and hyperalgesia following heat/capsaicin sensitization. J Pain 2003; 4:400–6.
Simpson DM, Olney R, McArthur JC, Khan A, Godbold J, Ebel-Frommer K. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. Neurology 2000;54:2115–9.
Simpson DM, McArthur JC, Olney R, Ross D, Batrrett P, Baird BJ. A multicenter, double-blind, randomized, placebo-controlled evaluation of lamotrigine in adult subjects with painful HIV-associated peripheral neuropathy. Neurology 2002;58(Suppl. 3):A407.
Tanelian DL, MacIver MB. Analgesic concentrations of lidocaine suppress tonic A-delta and C fiber discharges produced by acute injury. Anesthesiology 1991;74:934–6.
Verdugo R, Ochoa JL. Quantitative somatosensory thermotest: a key method for functional evaluation of small calibre afferent channels. Brain 1992;115:893–913.
Wallace MS, Grubbs D. Effects of oral desipramine on capsaicin induced hyperalgesia. Anesth Analg 2002;95:973–8.
Wallace MS, Laitin S, Licht D, Yaksh TL. Concentration-effect relations for intravenous lidocaine infusions in human volunteers: effect on acute sensory thresholds and capsaicin-evoked hyperpathia. Anesthesiology 1997;86:1262–72.
Wallace MS, Rowbotham M, Bennett GJ, Jensen TS, Pladna R, Quessy S. A multicenter, double-blind, randomized, placebo-controlled crossover, evaluation of a short course of 4030W92 in patients with chronic neuropathic pain. J Pain 2001a;3:227–33.
Wallace MS, Ridgeway B, Leung A, Schulteis G, Yaksh TL. Concentration-effect relationship for intravenous alfentanil and ketamine infusions in human volunteers. Effects upon acute sensory thresholds and capsaicin evoked hyperpathia. J Pain 2001b;2:A724.
Wallace MS, Ridgeway B, Leung A, Schulteis G, Yaksh TL. Concentration-effect relationships for intravenous alfentanil and ketamine infusions in human volunteers: effects upon acute thresholds and capsaicin-evoked hyperpathia. J Clin Pharmacol 2002;42:70–80.
Wallace MS, Braun J, Schulteis G. Post-delivery of alfentanil and ketamine has no effect on intradermal capsaicin induced pain and hyperalgesia. Clin J Pain 2003;18:373–9.
Webb JK, Kamali F. Analgesic effects of lamotrigine and phenytoin on cold-induced pain: a crossover placebo-controlled study in healthy volunteers. Pain 1998;76:357–63.
Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 1997;73:223–30.