

Effects of the 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid/kainate antagonist LY293558 on spontaneous and evoked postoperative pain

Background: Previous studies suggest that 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate antagonists reduce experimentally induced pain. There have been no studies of AMPA/kainate antagonists in clinical pain.

Methods: Analgesic efficacy of intravenous LY293558 (0.4 or 1.2 mg/kg) was compared with that of intravenous ketorolac tromethamine (INN, ketorolac; 30 mg) and placebo in a randomized, double-blind, parallel-group study after oral surgery (n = 70). Study drugs were administered at the onset of moderate pain; pain intensity and relief were measured for 240 minutes.

Results: High-dose LY293558 and ketorolac tromethamine were superior to placebo ($P < .05$) for pain evoked by mouth opening and one of several measures of spontaneous pain: SPID240 \pm SEM for pain evoked by mouth opening was highest for ketorolac tromethamine (151 \pm 58), intermediate for high-dose LY293558 (-45 \pm 35), and least for low-dose LY293558 (-151 \pm 39) and placebo (-162 \pm 50). High-dose LY293558 was superior to placebo at individual time points (45 to 240 minutes) for pain evoked by mouth opening but not for spontaneous pain. The spontaneous summed pain intensity difference over 240 minutes (SPID240 \pm SEM) was highest for ketorolac tromethamine (303 \pm 84), intermediate for high-dose LY293558 (-51 \pm 40) and low-dose LY293558 (-96 \pm 45), and least for placebo (-180 \pm 24). LY293558 was well tolerated, with dose-dependent and reversible side effects including hazy vision in 20% of patients and sedation in 15%.

Conclusions: This is the first evidence that an AMPA/kainate antagonist reduces clinical pain. Tests of evoked pain may be more sensitive to certain analgesics than those of spontaneous pain. The evaluation of evoked pain as an outcome measure in analgesic trials may identify potentially useful compounds otherwise missed if only spontaneous pain is evaluated. (Clin Pharmacol Ther 2000;68:320-7.)

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Several recent animal studies suggest that modulation of the glutamatergic, ionotropic, non-*N*-methyl-D-aspartate 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptors can significantly affect pain transmission at diverse targets in the nervous system.¹⁻⁶ Analgesia after intrathecal administration of the glutamate antagonist 2,3-dioxo-6-nitro-7-sulfamoylbenzo (f) quinoxaline² supports a site of action at AMPA/kainate receptors in the superficial laminae of the spinal dorsal horn.⁷ In addition to this spinal action, injection of the glutamate antagonist 6-cyano-7-nitroquinoxaline-2,3-dione into the rat hindpaw reverses hyperalgesia and allodynia caused by pharmacologic activation of

AMPA and kainate receptors, thus suggesting a peripheral action.⁸ Finally, the ubiquity of AMPA/kainate receptors in the brain⁹ leaves open the possibility that their antagonists may mediate analgesia by blocking excitatory neurotransmission at supraspinal sites.

We recently reported on the safety and analgesic efficacy of the AMPA/kainate receptor antagonist LY293558 in normal human volunteers.¹⁰ Side effects of hazy vision and sedation were frequent but mild, dose-related, and reversible and rarely occurred at less than the maximal tolerated dose of 1.3 mg/kg administered intravenously. Preliminary data suggest that, after an intravenous dose, plasma concentrations of LY293558 peak at about 1 hour with an elimination half-life of approximately 30 minutes. Administration of either 33% or 100% of the maximal tolerated dose had no effect on brief thermal or electrical noxious stimuli but significantly reduced persistent pain and hyperalgesia compared with placebo after intradermal administration of the chemoirritant capsaicin. Analgesic efficacy at 33% of the maximal tolerated dose, a dose that produced no more side effects than placebo, strongly supported a specific pharmacologic mechanism. The effect of LY293558 on persistent pain and hyperalgesia induced by capsaicin but not on pain evoked by brief stimuli to normal skin parallels a similar pattern of action in the rat formalin model in which immediate pain behavior resulting from the injection is unaffected, but the delayed second phase of pain behavior is reduced.⁴ These observations suggest that LY293558 may suppress sensitization of peripheral and central nociceptors.¹¹ Because peripheral and central nociceptor sensitization is clinically important in pain resulting from postoperative tissue damage and inflammation,¹² this placebo-controlled study evaluates the analgesic efficacy and safety of LY293558 in comparison with ketorolac tromethamine (INN, ketorolac) as a positive control after oral surgery.

METHODS

This study was approved by the Institutional Review Board of the National Institute of Dental & Craniofacial Research. Eligible patients provided informed consent before study participation. Patients 18 years or older were eligible to participate if they required surgical removal of 2 to 4 third molars, at least one of which was a partial or full bony impaction that would normally be expected to produce moderate to severe postoperative pain. Potential subjects were excluded if they had a history of adverse reactions to any medications to be used in the study or any history of substance abuse or dependence. Subjects were excluded if they had taken an anal-

gesic, antiinflammatory, or central nervous system depressant drug (with the exception of midazolam used for the procedure) within 48 hours of oral surgery. Female patients of child-bearing potential who were pregnant, lactating, or not using oral or depot contraceptives were also excluded. Medical exclusions included a recent history of serious impairment of major organ function, as well as any form of psychiatric illness.

LY293558 ([3s,4aR,6R,8aR]-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl]decahydroisoquinolone-3-carboxylic acid monohydrate; Lilly Research Laboratories, Indianapolis, Ind) was reconstituted with 0.9% normal saline solution to a concentration of 10 mg/mL. Each single-dose infusion was administered over 15 minutes after dilution in 15 mL 0.9% normal saline solution.

After measuring baseline vital signs and inserting an intravenous cannula, oral surgery was performed after premedication with intravenous midazolam (titration of 1 to 5 mg) and regional anesthesia with 2% lidocaine in 1:100,000 epinephrine. A mucoperiosteal flap was raised and retracted, bone was removed, and the teeth were sectioned as needed to facilitate extraction. For each patient a summed surgical difficulty score was given after assigning each extracted third molar a score of 1 (simple extraction), 2 (soft tissue impaction), 3 (partial bony impaction), or 4 (full bony impaction).¹³ The extraction site was sutured and covered with gauze, and patients were transferred from the surgical suite to a monitored recovery room for observation and postoperative data collection.

Patients completed analgesic questionnaires every 20 minutes after surgery until the study drug was administered. On reaching two consecutive ratings of moderate pain or the first rating of severe pain ($t = 0$), patients were randomized to receive one of the four following intravenous infusions administered over 15 minutes: (1) 0.9% saline solution, (2) ketorolac tromethamine, 30 mg, (3) LY293558, 0.4 mg/kg, or (4) LY293558, 1.2 mg/kg. Data recorded after surgery until 4 hours after the study drug infusion was started included pain measures (see below), maximal voluntary mouth opening distance, drug-related adverse effects and their severity (rated as none [0], mild [1], moderate [2], or severe [3]), heart rate, blood pressure, oxygen saturation, and continuous monitoring with electrocardiography. Although no adverse cardiorespiratory effects were observed after administration of LY293558 in our previous study,¹⁰ measurement of heart rate, blood pressure, oxygen saturation, and continuous monitoring with electrocardiography were performed again in this study given the early phase of development of this drug. These data were recorded at 0, 5, 10, 15, 20, 25, 30, 45, 60, 90,

Table I. Summary of demographic characteristics

Treatment	Sex		Height (cm)	Weight (kg)	Midazolam (mg)	Lidocaine (mg)	Surgical difficulty*
	Male	Female					
Placebo	12	8	169.9 (1.7)	69.8 (3.0)	4.9 (0.1)	11.3 (0.4)	10.5 (0.4)
0.4 mg/kg LY293558	13	8	173.2 (2.2)	70.2 (2.2)	4.7 (0.1)	12.4 (0.4)	9.8 (0.5)
1.2 mg/kg LY293558	13	7	169.1 (1.9)	70.2 (3.4)	4.6 (0.1)	11.7 (0.3)	10.4 (0.4)
Ketorolac tromethamine	6	3	154.5 (18.3)	66.5 (8.4)	4.1 (0.5)	10.4 (1.3)	9.4 (1.2)

Data are mean values (SEM).

*Sum of the surgical difficulty for the teeth extracted scored as simple extraction (1), soft tissue impaction (2), partial bony impaction (3), or full bony impaction (4).

120, 150, 180, 210, and 240 minutes after the study drug infusion was started. The presence of residual local anesthesia was assessed at each time point by having study patients tap on each side of their lower lip and rate the sensation as "normal," "tingling," or "numb" (rated as 0, 1, or 2, respectively). Patients were excluded from the analysis if numbness persisted bilaterally at 3 hours after the start of oral surgery. The digit symbol substitution test, used to evaluate cognitive impairment,¹⁴ was performed by study patients before surgery and repeated 30 minutes after infusion of the study drug was started.

Pain intensity was recorded with a category scale scored as none [0], mild [1], moderate [2], or severe [3]; and also with a 100-mm visual analog scale (VAS) with a left anchor of "none" and a right anchor of "worst pain imaginable." Pain relief was recorded with a category scale scored as no relief [0], slight [1], moderate [2], a lot [3] or complete relief [4]; and also with a 100-mm VAS with a left anchor of "no relief" and a right anchor of "complete relief." To concurrently evaluate postoperative evoked pain, patients were asked (immediately after each spontaneous pain rating) to "open your mouth as wide as you can." Interincisal distance after maximal mouth opening and its elicited pain intensity was then recorded. Pain intensity was also rated at 24 and 48 hours after surgery, as were mouth opening and mouth opening pain at 48 hours after surgery.

At each pain measurement interview from 60 minutes to 240 minutes, study nurses offered patients one administration of a rescue analgesic (acetaminophen [INN, paracetamol] 600 mg by mouth with codeine 30 mg by mouth) if pain intensity was reduced (from $t = 0$) by less than 15 mm (VAS). Any patients receiving rescue analgesia continued to rate their pain intensity and relief at the designated time points. However, for purposes of analyzing study data, the pain intensity, pain relief, and mouth opening measures at the time of administration of the rescue analgesic were carried forward across all subsequent time points on the day of surgery.

Continuous measures of VAS pain intensity and relief, vital signs (heart rate, blood pressure and oxygen saturation), mouth opening distance, and digit symbol substitution test scores were analyzed at each time point by one-way ANOVA with post hoc Fisher's protected least significant difference test where indicated. Pain intensity and relief as measured by the category scale was analyzed by the nonparametric Kruskal-Wallis test with post hoc multiple comparisons. The summed pain intensity difference (SPID) was calculated with the formula:

$$\text{SPID} = \sum \text{PID}_t \times [\text{time elapsed since previous observation}]$$

in which $\text{PID}_t = \text{VAS pain at time } (t) - \text{VAS pain at time } (0)$. Total pain relief (TOTPAR) was calculated with the formula:

$$\text{TOTPAR} = \sum R_t \times [\text{time elapsed since previous observation}]$$

in which $R_t = \text{VAS relief at time } (t) - \text{VAS relief at time } (0)$. The SPID at 240 minutes (SPID240) and the TOTPAR at 240 minutes (TOTPAR240) were each calculated with individual patient data at each time point. However, VAS pain and VAS relief measurements observed at the time of rescue analgesic administration were entered also as the pain and relief measurements for each subsequent time point after rescue analgesic administration. The incidences of adverse effects were evaluated by χ^2 analysis.

A sample size of 20 subjects per group was calculated on the basis of a previous study with the oral surgery model¹⁵ to detect a 35% reduction in pain by drug compared with placebo with a power of 0.80. Given the previously observed magnitude of pain reduction by ketorolac tromethamine,¹⁶ we estimated the need for only 10 patients in the ketorolac tromethamine group.

RESULTS

A total of 72 patients were screened, were deemed eligible, and consented to the study. Two patients underwent oral surgery but had no development of moderate

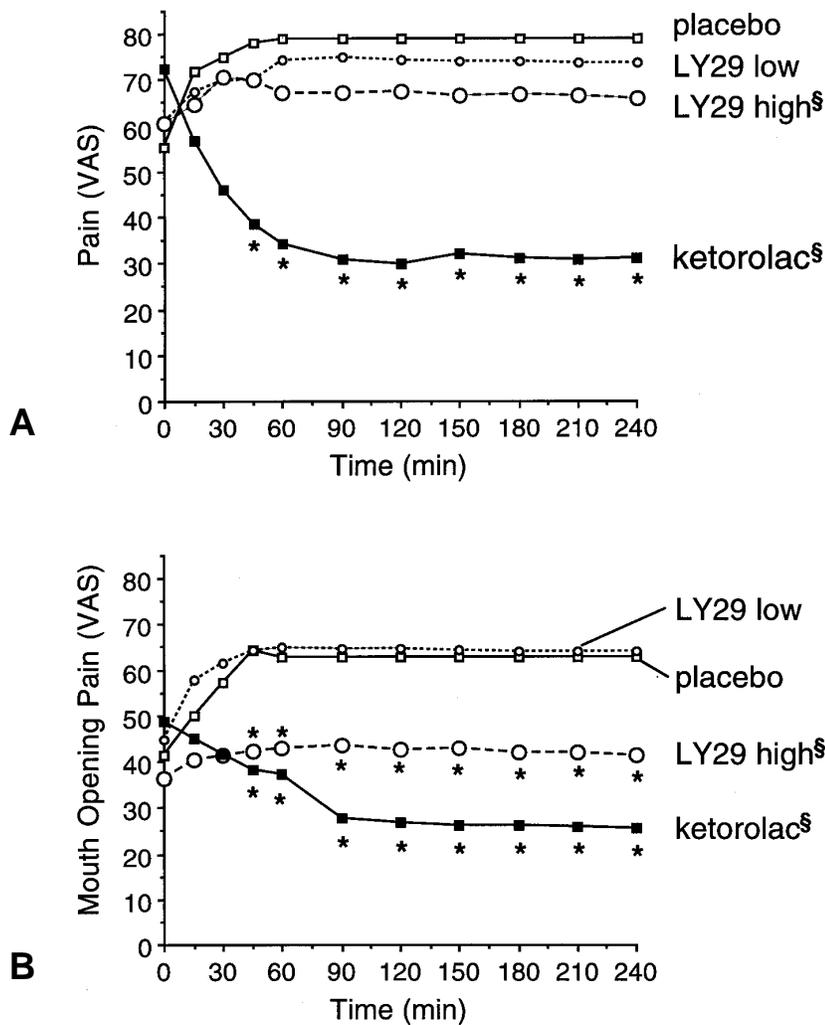


Fig 1. Pain intensity scores as measured by visual analog scale (VAS) after study drug administration ($t = 0$) for the 4 treatment groups. **A**, Spontaneous pain. **B**, Pain evoked by maximal voluntary mouth opening. * $P < .05$ compared with placebo. §Summed pain intensity difference over 240 minutes greater than for placebo, $P < .05$.

pain after operation and were thus not randomized to treatment. Seventy patients were randomized to treatment and completed the entire study. There were no significant differences across treatment groups in the categories of sex, height, weight, doses of midazolam and lidocaine used, and the surgical difficulty scores (Table I). Pain intensity measured by VAS increased coincident with the offset of anesthesia in the placebo group to reach a mean pain intensity of approximately 55 to 72 (of 100 mm maximum; Fig 1, A). Intravenous ketorolac tromethamine, 30 mg, significantly reduced spontaneous pain measured by VAS (compared with placebo, $P < .05$) from 45 to 240 minutes after the start of drug infusion

(Fig 1, A) and significantly increased the VAS summed pain intensity difference over the 240 minutes (SPID240; Table II). The VAS SPID240 for LY293558 was significantly greater than placebo at 1.2 mg/kg ($P < .05$) but was indistinguishable from placebo at 0.4 mg/kg. Pain measured by the category scale was significantly reduced (compared with placebo, $P < .05$) in the ketorolac tromethamine group from 60 to 240 minutes.

Preoperative mouth opening distances (mean 52.9 ± 1.6 mm) were significantly reduced ($P < .05$) in all treatment groups after surgery (Table II). Although maximal voluntary mouth opening caused no pain in any patients before operation, all individuals reported

pain on mouth opening after surgery. Administration of LY293558 (at 1.2 mg/kg) and of ketorolac tromethamine produced significant reductions (compared with placebo, $P < .05$) in pain intensity evoked by mouth opening from 45 to 240 minutes (Fig 1, B). For pain evoked by mouth opening, the summed pain intensity differences over the 240 minutes (SPID240 \pm SEM) were significantly greater ($P < .05$) than placebo for ketorolac tromethamine and LY293558 at 1.2 mg/kg. LY293558 (at both 0.4 and 1.2 mg/kg) and ketorolac tromethamine improved mouth opening distance (compared with placebo, $P < .05$) at 60 minutes (Table II). These differences persisted for LY293558 (at 0.4 mg/kg) and ketorolac tromethamine until 240 minutes.

Pain relief in the ketorolac tromethamine group was significantly greater than placebo ($P < .05$) from 30 to 240 minutes when measured by VAS and from 60 to 240 minutes when measured by the category scale (Table II). Total pain relief over the 240 minutes (TOTPAR240 \pm SEM) was greater for ketorolac tromethamine than for placebo, 0.4 mg/kg LY293558 or 1.2 mg/kg LY293558 (Table II). TOTPAR240 was significantly greater than placebo only in the ketorolac tromethamine group ($P < .05$).

There were no significant differences across treatment groups in heart rate, blood pressure, oxygen saturation, and cognitive function (data not shown). No major adverse events were encountered in the study. Although there were no statistically significant differences in side effects across treatment groups (Table III), there was a nonsignificant trend for the occurrence of sedation and visual symptoms (particularly in the 1.2 mg/kg LY293558 group) that also occurred in our previous study.¹⁰ To determine whether side effects influenced pain relief, spontaneous and mouth opening-evoked SPID240 scores in patients from the 1.2 mg/kg LY293558 group who experienced no side effects were compared with those who experienced any side effects and showed no consistent relationship between side effects and pain. For spontaneous pain there was a nonsignificant trend toward increased SPID240 in patients who experienced no side effects (no side effects: 41.2 ± 36.1 ; any side effects: -56.8 ± 59.7). For evoked pain there was a nonsignificant trend toward increased SPID240 in patients who experienced any side effects (no side effects: -20.6 ± 73.4 ; any side effects: 93.3 ± 47.7).

All patients in the placebo group and all but one patient in the LY293558 (0.4 mg/kg) group required rescue analgesia at 60 minutes. In the LY293558 (1.2 mg/kg) group, all but two patients required rescue analgesia, and one patient received rescue analgesia later at

120 minutes. In the ketorolac tromethamine group, all but four patients required rescue analgesia, and two patients received rescue analgesia later at 90 and 180 minutes.

DISCUSSION

To our knowledge this is the first trial of an AMPA/kainate receptor antagonist in clinical pain. These results demonstrate that, after oral surgery, LY293558 reduced postoperative pain evoked by mouth opening and exerted a small effect on spontaneous pain that was statistically significant only for the VAS pain intensity SPID240. Single doses of LY293558 appear safe in human beings, although administration is associated with dose-dependent and reversible side effects such as hazy vision and sedation. The occurrence of side effects did not appear to bias patients with regard to reporting reductions in pain.

Data on pain and mouth opening distance are carried forward to all time points subsequent to the time of rescue analgesic administration across all treatment groups. Therefore carryover data for patients who have received rescue analgesia do not reflect "real-time" responses at these subsequent time points. These imputed data may dilute effects observed from patients who did not receive rescue analgesia. Nevertheless, a reduction of mouth opening pain by LY293558 was also observed at 45 and 60 minutes, at a time before any patients received rescue medication.

As in previous oral surgery studies, we observed a postoperative reduction in voluntary mouth opening distance believed to be due to local inflammation and related trismus.¹⁷ The observation that LY293558 produced a differential effect on spontaneous pain and pain evoked by mouth opening suggests the involvement of different mechanisms. It is likely that the observed movement-evoked pain is largely due to peripheral changes associated with local inflammation. However, evidence exists to suggest that sensitization of second-order dorsal horn neurons may also play an important role in the postoperative period. In particular, Dahl et al¹⁸ observed hyperalgesic and allodynic responses to sural nerve stimulation, which bypasses peripheral tissues, in patients after laparotomy. Similar to our results, Stubhaug et al¹⁹ reported that the *N*-methyl-D-aspartate antagonist ketamine reduces hyperalgesia around a surgical wound for up to 7 days after operation whereas effects on spontaneous pain intensity are only observed on the day of surgery.

In view of our finding that movement-evoked pain is especially sensitive to this AMPA/kainate receptor blocker, we suggest that this variable be measured in

Table II. Measures of postoperative pain intensity, pain relief, maximal voluntary mouth opening distance, and intensity of pain evoked by mouth opening

	Ratings at single time points					
	0 min	30 min	60 min	120 min	180 min	240 min
Pain (VAS)						
Placebo	55.1 (2.6)	74.65 (4.5)	78.75 (4.4)	78.75 (4.4)	78.75 (4.4)	78.75 (4.4)
0.4 mg/kg LY293558	60.9 (4.5)	69.7 (6.9)	74.3 (6.1)	74.1 (6.2)	73.9 (6.3)	73.5 (6.5)
1.2 mg/kg LY293558	60.4 (3.3)	70.6 (5.1)	67.1 (5.1)	67.2 (5.1)	66.7 (5.2)	65.8 (5.7)
Ketorolac tromethamine	72.3 (6.0)	45.9 (11.1)	34.2 (8.7)*	29.7 (8.5)*	31.0 (9.0)*	31.1 (9.0)*
Pain (CAT)						
Placebo	2.2 (0.1)	2.6 (0.1)	2.7 (0.1)	2.7 (0.1)	2.7 (0.1)	2.7 (0.1)
0.4 mg/kg LY293558	2.2 (0.1)	2.4 (1.2)	2.5 (0.1)	2.5 (0.1)	2.5 (0.1)	2.4 (0.2)
1.2 mg/kg LY293558	2.2 (0.1)	2.4 (0.2)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)	2.4 (0.2)
Ketorolac tromethamine	2.3 (0.2)	1.7 (0.3)	1.2 (0.3)*	1.2 (0.3)*	1.0 (0.3)*	1.1 (0.3)*
Relief (VAS)						
Placebo	—	4.1 (1.8)	3.1 (2.0)	3.1 (2.0)	3.1 (2.0)	3.1 (2.0)
0.4 mg/kg LY293558	—	11.7 (4.9)	10.4 (4.3)	10.9 (4.6)	11.1 (4.7)	11.5 (5.1)
1.2 mg/kg LY293558	—	9.8 (3.2)	10.6 (3.2)	10.7 (3.5)	14.1 (5.3)	13.0 (5.1)
Ketorolac tromethamine	—	43.0 (12.3)*	53.2 (11.0)*	58.6 (11.6)*	61.2 (12.2)*	59.9 (11.7)*
Relief (CAT)						
Placebo	—	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
0.4 mg/kg LY293558	—	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.5 (0.2)
1.2 mg/kg LY293558	—	0.5 (0.2)	0.5 (0.2)	0.4 (0.2)	0.6 (0.2)	0.5 (0.2)
Ketorolac tromethamine	—	1.6 (0.5)	2.0 (0.4)*	2.1 (0.4)*	2.3 (0.5)*	2.3 (0.5)*
Mouth opening (mm)						
Placebo	34.9 (1.7)	30.7 (1.6)	28.0 (1.2)	28.0 (1.2)	28.0 (1.2)	28.0 (1.2)
0.4 mg/kg LY293558	36.9 (2.0)	33.6 (2.0)	33.7 (2.0)*	33.6 (2.0)*	33.7 (2.0)*	33.9 (2.0)*
1.2 mg/kg LY293558	30.9 (1.1)	32.3 (1.4)	33.2 (1.7)*	33.0 (1.7)	33.0 (1.8)	33.0 (1.8)
Ketorolac tromethamine	32.4 (3.3)	36.3 (4.0)	38.1 (3.4)*	36.3 (3.6)*	38.3 (3.9)*	37.6 (3.8)*
Opening pain (VAS)						
Placebo	41.3 (4.8)	57.0 (5.1)	62.6 (6.5)	62.6 (6.5)	62.6 (6.5)	62.6 (6.5)
0.4 mg/kg LY293558	44.6 (6.2)	61.4 (7.6)	64.9 (6.9)	64.4 (7.0)	64.0 (7.2)	64.0 (7.2)
1.2 mg/kg LY293558	36.5 (5.7)	41.2 (6.0)	42.9 (6.2)*	42.6 (6.2)*	41.8 (6.4)*	41.4 (6.5)*
Ketorolac tromethamine	48.7 (7.2)	41.7 (9.3)	37.2 (8.5)*	26.6 (7.6)*	26.1 (9.0)*	25.4 (8.9)*

Data are mean values (SEM).
**P* < .05 compared with placebo.

Table III. Incidence of adverse effects

Treatment	No. of patients						
	With no side effects	With any side effect ≥ moderate	With visual disturbance	With sedation	With headache	With nausea	With other side effect
Placebo (n = 20)	12	7	0	1	6	0	4
0.4 mg/kg LY293558 (n = 21)	11	7	1	2	6	1	1
1.2 mg/kg LY293558 (n = 20)	7	7	4	3	8	1	3
Ketorolac tromethamine (n = 9)	6	3	0	0	3	0	1

postoperative studies of other compounds. Because movement-evoked pain limits rehabilitative efforts and patients' everyday activities, a drug that disproportionately blocked movement-evoked pain would be poten-

tially valuable but might be dropped early in development after negative acute pain studies that assessed only pain at rest. Analgesic researchers have rarely systematically compared pain at rest with movement-evoked

pain. We are not aware of studies of movement-evoked pain in the dental extraction model. Many previous analgesic studies in patients who underwent thoracic, abdominal, or orthopedic surgery have combined individuals who reported on pain at rest as the primary outcome with others who reported movement-evoked pain (Beaver W. Personal communication. 1999).²⁰ In these studies, the study nurse chose either a resting state or a pain-provoking maneuver to adjust baseline pain to a moderate-to-severe level because this range is optimal for discriminating effective analgesics from controls. Recently, Tverskoy et al²¹⁻²³ have systematically assessed pain at rest and movement-evoked pain in several studies examining discrete mechanisms of pain after hernia repair and hysterectomy. Using different treatments from ours, they found an effect opposite to our own, that pain evoked by turning in bed or standing was more resistant than pain at rest to either local anesthesia of the surgical wound²² or intravenous alfentanil.²³ If replicated, our finding that movement-evoked pain is more sensitive to AMPA/kainate blockers than rest pain would suggest that these drugs might be complementary to opioid analgesics.

The minimal effect on spontaneous pain compared with current standard therapies questions the clinical utility of this particular compound for acute postoperative pain. However, together with our previous study,¹⁰ these data provide further evidence that AMPA/kainate receptor antagonism provides analgesia in human beings. Further development of this class of agents requires the clinical evaluation of compounds with a more favorable therapeutic ratio. An ideal compound would target the AMPA/kainate receptor subtype(s) that selectively modulate nociception. The AMPA/kainate receptor system is divided into AMPA-preferring (GluR1-4) and kainate-preferring (GluR 5-7, KA 1-2) receptors.⁹ LY293558 has been described as a relatively potent antagonist at AMPA (GluR1-4) receptors²⁴ and at kainate (GluR5) receptors.²⁵ LY293558 also weakly antagonizes human GluR7 and KA2 receptors²⁶ and has no activity at human GluR6 receptors.²⁵ Selective AMPA antagonists such as 6-cyano-7-nitroquinoxaline-2,3-dione²⁷ and more recently YM872²⁸ have been shown to produce analgesia in chronic and acute animal pain models, respectively. However, Simmons et al⁴ showed that LY382884, a selective blocker of the GluR5 receptor, produced superior analgesia, whereas AMPA receptor blockade by LY300164 produced greater side effects such as ataxia. Data from Stanfa and Dickenson²⁹ further demonstrate the antinociceptive effects of GluR5 antagonism with LY382884 in both normal and carrageenan-inflamed rats. The finding that

GluR5 receptor knockout mice are able to develop pain and hyperalgesia similar to wild-type mice differs from these pharmacologic studies.³⁰ This finding suggests that there are multiple mechanisms of nociception and that GluR5 antagonists must be supplemented by other analgesics.

In conclusion, this study provides further evidence of safety of the AMPA/kainate antagonist LY293558 in human beings. Future clinical studies should focus on more selective AMPA or kainate receptor antagonists likely to have an analgesic therapeutic profile superior to that of LY293558.

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