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Interaction of Intrathecally Infused Morphine and Lidocaine in Rats (Part I)

Synergistic Antinociceptive Effects

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Background: **Synergistic antinociception of opioids and local anesthetics has been established in bolus injections but not in long-term use. The somatic and visceral antinociceptive effects of intrathecally infused morphine or lidocaine were characterized, and the nature of the interaction of those agents in rats was evaluated.**

Methods: **Intrathecal catheters were implanted in rats. Morphine (0.3 to 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$), lidocaine (30–1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$), a combination of those, or saline was infused intrathecally at a constant rate of 1 $\mu l/h$ for 6 days. The tail flick and colorectal distension tests were used to measure the somatic and visceral antinociceptive effects, respectively. Nociceptive tests and motor function tests were repeated on days 1, 2, 3, 4, and 6. Isobolographic analysis was performed on the results of the tail flick test to determine the magnitude of the interaction.**

Results: **Intrathecally infused morphine produced dose-dependent antinociceptive effects in both the tail flick and the colorectal distension tests. Morphine showed a lower peak percentage maximum possible effect (%MPE) in the colorectal distension test than in the tail flick test. Intrathecal lidocaine also produced dose-dependent antinociceptive effects. Lidocaine infusion at 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ caused motor impairment. Coinfusion of morphine 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and lidocaine 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, which had no effects by themselves, significantly increased the percentage maximum possible effects ($P < 0.01$). Coinfused lidocaine potentiated the duration and the magnitude of morphine antinociception. Isobolographic analysis of the tail flick test on day 1 showed a synergistic interaction between morphine and lidocaine.**

Conclusions: **Morphine and lidocaine intrathecally coadministered synergistically potentiated the antinociceptive effects of each other. That coinfusion dramatically potentiated visceral antinociception, whereas the infusion of morphine alone showed little visceral antinociception. (Key words: Analgesia; potentiation; spinal.)**

CONTINUOUS infusion of combinations of opioids and local anesthetics has been used widely to treat many kinds of postoperative,[1–7] cancer,[8,9] and labor pain.[10–12] Despite many clinical studies of the analgesic effects of those combinations, the results are conflicting: from no additional analgesia[13–15] to potentiated analgesia.[1,2,10] These different results, in part, reflect difficulties in comparing analgesic effects in patients with dynamic pain states, different pain sources and intensity, and different perceptions and expressions of pain.

Synergistic antinociception after epidural or intrathecal coadministration of opioids and local anesthetics has been established in animal experiments.[13–18] However, those studies investigated the interaction after bolus injections of those combinations rather than after continuous infusions. The characteristic differences between bolus injection and continuous infusion, such as volume, dose of administered agents, and effective duration, presumably will have an effect on the coadministration. However, the antinociceptive effects of continuously coinfused opioids and local anesthetics at the spinal level have not been elucidated clearly.

In long-term pain control, the ability to provide analgesia for visceral pain is important because long-lasting pain, including cancer-related pain, frequently involves visceral organs.[19,20] Visceral processing systems in the spinal cord have distinctive anatomic and physiologic

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features compared with somatic processing,[21–23] and those may influence the analgesia of intrathecally administered agents. In fact, recent studies showed that different magnitudes of visceral antinociception or somatic antinociception are produced, depending on the type of analgesic agents,[16,24] and that synergistic visceral antinociception is associated with administered agents or their combinations.[25–27] However, the nature of visceral antinociception at the spinal level with continuously administered opioids and local anesthetics, not to mention combinations of those, has not been clarified; and neither somatic nor visceral antinociceptive responses during intrathecal local anesthetic infusion have been evaluated.

This study was designed to characterize both the somatic and the visceral antinociception of intrathecally infused morphine or lidocaine and to evaluate the nature of the interaction.

Materials and Methods

Male Sprague-Dawley rats (Clea Japan, Tokyo, Japan) were used for this study with approval of the Animal Research and Use Committee of Shimane Medical University. Animals were housed individually in standard cages at room temperature on a 12-h light–dark schedule with free access to food and water. To reduce the effects of handling during nociceptive responses, all animals were handled and trained in the test situation for at least 4 days before intrathecal catheterization. Tests were administered during the light cycle.

Intrathecal Catheter Placement

To make the intrathecal catheter, sections of polyethylene tubing PE-60 (2 cm), PE-20 (6 cm), and PE-10 (2 cm) (Beckton-Dickinson, Sparks, MD) were connected to each other, resulting in a catheter with a decreasing-diameter profile. The PE-60 end of the profiled catheter was connected to an Alzet miniosmotic pump (model 2001; Alza, Palo Alto, CA) that was filled with 250 μl of a drug solution or normal saline. The pump was immersed in a 37°C normal saline bath. The drug infusion was started 6–8 h before catheter implantation to prefill the catheter so drug delivery to the spinal cord began soon after the catheter was implanted.

Catheters were implanted using an aseptic technique during halothane anesthesia induction. For intrathecal catheterization, anesthesia was induced by placing the rat in a closed box containing 4% halothane in oxygen and was maintained with 2% halothane *via* a loose-fitting plastic mask. The skin of the back was shaved in the lumbar region, and 10% povidone iodine was applied. To flex the lower thoracic and lumbar vertebral column during surgery, a foam block was placed under the animal's abdomen. A midline skin incision was made over the spinous processes of the L3 and L5 vertebrae. The fascia was opened and superficial muscles around the spinous process were dissected and retracted laterally. Using fine forceps, the ligament was pierced. After opening the dura with a 30-gauge needle hook at the fourth lumbar vertebral space, the PE-10 end of the intrathecal catheter was inserted in the rostral direction to position the tip at the level of the lumbar enlargement. The catheter was fixed on muscles by two sutures to maintain it in the intrathecal space. A drop of surgical glue was applied over the site where the catheter entered the epidural space. The miniosmotic pump, attached to the PE-60 end, was implanted subcutaneously on the back. Cefazolin sodium (100 mg) was injected intramuscularly and the skin incision was closed.

Nociceptive Tests

The tail flick (TF) test was used to measure the response to a noxious somatic stimulus using a TF instrument (model-DS20; Ugo Basile, Comerio-Varese, Italy). The latency from the onset of the heat stimulus to the withdrawal from a heat source (a 100-W projector lamp) that was focused on a distal segment of the tail was recorded. The apparatus was calibrated to provide an average baseline latency of approximately 4 s. A cutoff time of 10 s was used to avoid tissue damage.

The colorectal distension (CD) test was used to measure the response to a noxious visceral stimulus. The CD apparatus and methods were modified from those of Ness and Gebhart.[28] This test involves inflation with air of an 8-cm, flexible, latex balloon that has been manually inserted into the descending colon and rectum. The system consists of two parts: a large proximal stimulating balloon and a small distal sensing balloon. Stimulating- and sensing-balloon pressures were monitored continuously and separately by in-line pressure transducers and recorded (Rectigraph; Sanei, Tokyo, Japan). The balloons were inserted intraanally in the descending colon and rectum during light halothane anesthesia. Animals were tested while awake after a recovery time of 20 min from halothane anesthesia. Pressure within the intracolonic stimulating balloon was steadily increased at a rate of 2.5 mmHg/s, beginning at 0 mmHg, until abdominal muscles contracted repeatedly and a rapid increase in

the pressure (spike-like waves) in the sensing balloon was detected. The minimal pressure in the stimulating balloon at which the increase of the pressure in the sensing balloon was triggered was defined as the threshold response for visceral nociception in this test. A cutoff distension pressure of 60 mmHg was used to prevent tissue damage.

The TF and CD tests were performed sequentially at the same time each day, with a 2-min interval between each test. In a preliminary study, TF latencies with and without the CD test were measured, and CD thresholds with and without TF tests were measured in the same rats using the same interval. The presence of one test did not influence the threshold of the other.

Motor Function Tests

Motor function was assessed by bilaterally grading the motor block in the lower limbs as follows: 0 = no visible limb weakness and normal gait; 1 = the rat could move the limb but not support normal posture; and 2 = the limb was flaccid with no detectable resistance to extension of the limbs. The normal baseline motor block score was 0, and the motor block score with bilateral complete blockade was 2 + 2 = 4.

Experimental Protocol

On the day of surgery, the CD balloon was inserted manually during light halothane anesthesia, and the rat was allowed to recover from the halothane for at least 20 min before baseline values were determined for both the TF and the CD tests. After determination of the baseline values, the intrathecal catheter and mini-osmotic pump were implanted. The animals were designated into 12 equal groups (n = 7 each). One of the following four regimens with an intrathecally delivered constant infusion rate of 1 μl/h for 6 days by the miniosmotic pump was used in each group. The mean body weights of the animals before catheter implantation are noted in parentheses.

1. Morphine hydrochloride: 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (315 ± 9 (± SD) g), 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (307 ± 5 g), 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (313 ± 11 g), 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (309 ± 10 g), and 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (317 ± 11 g)
2. Lidocaine hydrochloride: 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (313 ± 6 g), 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (310 ± 8 g), 600 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (308 ± 5 g), and 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (314 ± 10 g)
3. A combination of morphine hydrochloride + lidocaine hydrochloride: 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ + 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (313 ± 11 g) and 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ + 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (316 ± 9 g)
4. Normal saline (313 ± 9 g)

These doses and combinations were determined after preliminary studies to define appropriate dose ranges. Morphine at 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and lidocaine at 30 and 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ were used for a subdose combination because those doses did not produce an increase in the percentage maximum possible error (%MPE) in any animals in the pilot study. To perform isobolographic analysis, the dose ratio of the combination was fixed at a morphine:lidocaine ratio of 1:200 by adjusting the concentrations of solutions. Additional combination doses with 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine + 60 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine (311 ± 11 g); 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine + 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine (317 ± 12 g); 0.75 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine + 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine (315 ± 11 g); and 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine + 600 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine (306 ± 6 g) were used to conduct isobolographic analyses.

Nociceptive tests and motor function tests were repeated on days 1, 2, 3, 4, and 6 during the intrathecal infusion protocol. Animals were used for a single experiment and then killed. Animals showing any neurologic deficits, infection, or other health problems after implantation were excluded from this experiment. The location of the distal end of the catheter and the spread of drug solution were verified at the conclusion of an experiment by injecting indigocarmine dye and by postmortem examination of the spinal cord.

Statistical Analysis

Data obtained from animals in which the dye failed to stain the lumbar intrathecal space or in which the spinal cord had observable damage were not included in the data analysis. Animals exhibiting any neurologic deficits, infection, or other health problems during experiments were also excluded from data analysis.

To analyze changes in antinociceptive effects, TF latency and CD threshold were converted to %MPE = (postdrug value − baseline value)/(cutoff value − baseline value) × 100%. Cutoff values were 10 s and 60 mmHg in TF and CD tests, respectively. Three responses for each rat were averaged and a mean %MPE was calculated at each dose and time point. Motor block scores are presented as median and tenth and ninetieth percentiles, and the other data are presented as mean ± SD. Changes in %MPE after intrathecal injection were analyzed with analysis of variance for repeated measures

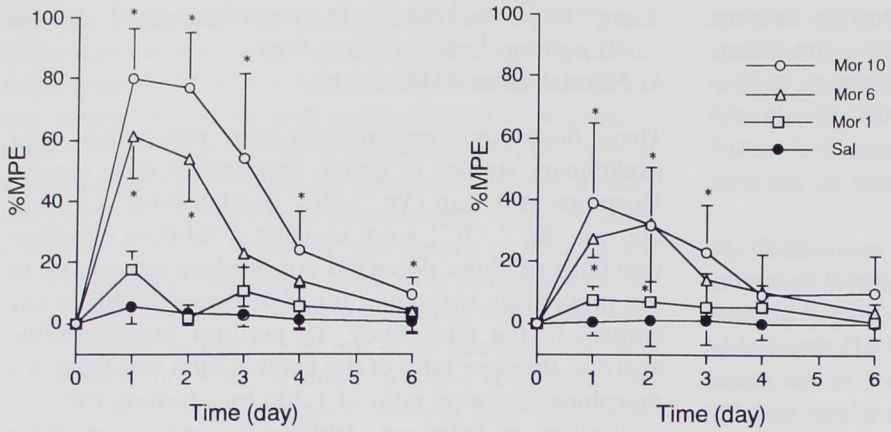

Fig. 1. The time course of effects on percentage maximum possible effect in the tail flick test (*left*) and the colorectal distension test (*right*) during intrathecal infusion of morphine (Mor) at the rate of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6), 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 7), or 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 7) or of saline (Sal) (n = 7) for 6 days. Data are presented as the mean ± SD. *Significantly different from Sal.

followed by Scheffé's *post hoc* test for between-group comparison. Differences in motor block scores were analyzed by the Mann–Whitney U test. A P value < 0.05 was considered significant.

Isobolographic Analysis

To determine whether the antinociceptive interactions of morphine and lidocaine were subadditive, additive, or synergistic, isobolographic analysis was performed from results on day 1 using the method of Tallarida *et al.*[29] First, three dose–effect curves were determined: two with morphine or lidocaine administered alone and a third with a combination of a fixed-dose ratio of morphine and lidocaine. Four or five points (n = 6 or 7 for each) were used to determine each dose–effect curve. The dose–effect curves and the median effective dose (ED_{50}) values and 95% confidence intervals (CIs) were computed.[30] The resulting ED_{50} values were plotted in the form of an isobologram. The ED_{50} values and CIs for each drug alone were plotted on the x and y axes, and the ED_{50} value and the CI for the combination were placed in the dose field. The theoretical additive line is represented by the diagonal line connecting the ED_{50} doses on the x and y axes, and the theoretical additive point was calculated according to the method described by Tallarida *et al.*[29] Drug interactions are considered to be synergistic if the combination ED_{50} point is below the theoretical additive line. Statistical significance between theoretical additive points and experimental points were evaluated according to Tallarida.[31]

To obtain a value for describing the magnitude of the interaction, a total fraction value was calculated as described by Roerig *et al.*[32] The ED_{50} values of the drug given alone were assigned a total fraction value of 1. The total fraction was calculated as (ED_{50} dose of morphine in combination/ED_{50} value for morphine alone) + (ED_{50} dose of lidocaine in combination/ED_{50} value for lidocaine alone). Values near 1 indicate an additive interaction; values <1 imply a supra-additive interaction.

Results

Eight of 112 rats were excluded from data analysis because of infusion or catheter failure, and two rats were excluded because of neurologic impairment or other health problems, resulting in a study population of 102 rats. The baseline values in the TF and CD tests were not significantly different among groups.

Morphine Alone

Intrathecally infused morphine produced dose-dependent antinociceptive effects in both TF and CD tests, with peak effects evident on day 1, whereas saline produced no change in %MPEs (fig. 1). The increases in %MPEs returned to nearly baseline levels (<20 %MPE) on day 4, except for the 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine infusion. Of particular interest, the peak %MPE in the CD test was much lower than that in the TF test.

None of the morphine doses tested or saline showed any evidence of motor impairment.

Lidocaine Alone

Intrathecal lidocaine also produced dose-dependent antinociceptive effects in both the TF and the CD tests (fig. 2). Peak %MPEs in the TF and CD tests were 85% on day 1 and 70% on day 2, respectively, during infusion of 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine (fig. 2). The significant increases ($P < 0.05$) of %MPE in the TF and CD tests returned to baseline levels on day 3, with 600

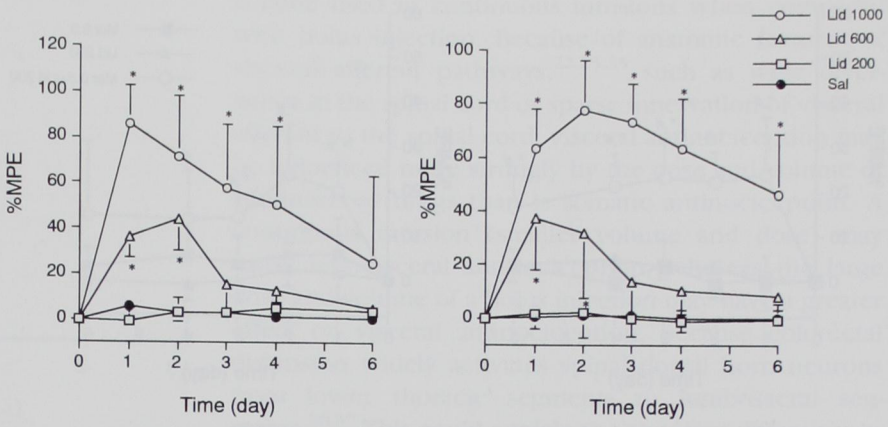

Fig. 2. The time course of effects on percentage maximum possible effect in the tail flick test (*left*) and the colorectal distension test (*right*) during intrathecal infusion of lidocaine (Lid) at the rate of 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6), 600 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6), or 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6) or of saline (Sal) for 6 days. Data are presented as the mean ± SD. *Significantly different from Sal.

$\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine and on day 5 with 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine.

Because motor block by lidocaine could confuse interpretation of %MPE data, we also evaluated the occurrence of motor block in these animals. With the exception of two animals that showed a partial block (motor block score = 1 or 2) on day 1 and day 2 with an infusion of 600 $\mu g \cdot kg^{-1} \cdot h^{-1}$, motor impairment was not observed with lidocaine infusions at 600 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or less during the 6 days of observation (table 1). All the animals showed motor impairment after infusion of 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine. The motor impairment gradually decreased from day 2 (table 1). However, slight motor impairment remained with 1,000 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine on day 6.

Coinfusion of Morphine and Lidocaine

Infusion of a combination of 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine and 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine, each of which had no effect by itself, significantly increased %MPEs ($P < 0.01$) compared with the same dose of morphine or lidocaine alone in both the TF and the CD tests (fig. 3). The potentiated antinociceptive effects on the TF and the CD tests lasted for 6 days and 3 days, respectively. As shown in figure 4, coinfusion of a very low dose of 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine potentiated the magnitude and duration of the antinociception caused by 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine, which alone produced antinociception.

The isobologram of the TF data on day 1, illustrated in figure 5, shows that the experimentally derived ED_{50} value and CI decreased below the theoretical dose-additive line, and the CIs of the theoretical additive point and those of the experimental point did not overlap (fig. 5). This result indicates a significant difference between the experimental ED_{50} point and the theoretically additive ED_{50} point ($P < 0.05$) and a synergistic interaction between morphine and lidocaine during intrathecal infusion in the TF test.

The total fraction value in the TF test on day 1 was 0.31, which was less than 1, indicating a synergistic interaction. The absence of dose-dependent effects on the CD test of morphine with the infusions used in this study made it impossible to perform an isobolographic analysis of the CD test.

Coinfusion of morphine and lidocaine at the doses used in this study resulted in no significant increase in motor impairment.

Discussion

We found that continuous intrathecal coinfusion of morphine and lidocaine produced better antinociception against somatic and visceral noxious stimuli. Synergistic antinociceptive interactions, which have been

Table 1. Motor Block Score during Intrathecal Infusion of Morphine, Lidocaine, and Their Combination

Drug	Dose ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	Score		
		Day 1	Day 3	Day 6
Morphine	1	0 (0,0)	0 (0,0)	0 (0,0)
	6	0 (0,0)	0 (0,0)	0 (0,0)
	10	0 (0,0)	0 (0,0)	0 (0,0)
Lidocaine	200	0 (0,0)	0 (0,0)	0 (0,0)
	600	0 (0,1)	0 (0,0)	0 (0,0)
	1,000	2 (2,3.9)*	1.5 (1,2)*	0.5 (0,1.9)*
Morphine + lidocaine	0.3 + 200	0 (0,0)	0 (0,0)	0
	3 + 30	0 (0,0)	0 (0,0)	0 (0,0)
Saline		0 (0,0)	0 (0,0)	0 (0,0)

Values are median (10th, 90th percentiles).

* $P < 0.05$, *versus* saline group.

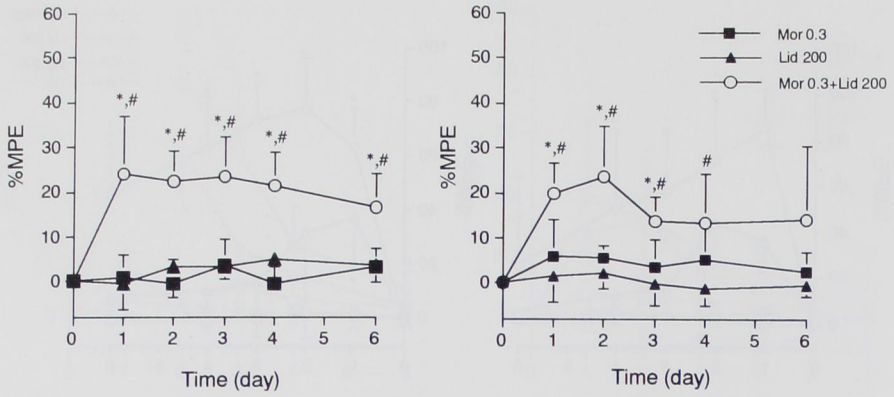

Fig. 3. The time course of effects on percentage maximum possible effect in the tail flick test (*left*) and the colorectal distension test (*right*) during intrathecal infusion of morphine (Mor) at 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6), lidocaine (Lid) at 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6), or the combination of those (n = 6) for 6 days. Data are presented as the mean ± SD. *Significantly different from 0.3 Mor. #Significantly different from 200 Lid.

well established with bolus injections of opioids and local anesthetics,[16–18] appear to be preserved during continuous coinfusion in which agents are administered in small volumes and low concentrations. The magnitude of the synergistic effects depends on the concentration of infused drugs when the infusion rate is constant. Isobolographic analysis and total fraction analysis in the TF test confirmed the synergistic interaction during somatic antinociception. We did not evaluate the interaction on visceral antinociception by isobolographic analysis, because the increase in %MPE in the CD test after intrathecal morphine infusion was less than 30%, even at peak times in the dose range used in this study, and the infused concentration of morphine is limited because of its solubility. However, strong potentiation of visceral antinociception during the coinfusion of morphine and lidocaine was shown in terms of an increase in %MPE in the CD test at each time point and in terms of a longer duration of the increase of %MPE and a time-course response of visceral antinociception that was comparable to that of somatic antinociception. In addition, visceral antinociceptive effects caused by the coinfusion of 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine and 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ lidocaine, which had no effects by themselves, may indicate synergistic antinociceptive effects on visceral and somatic stimuli. We believe that this study shows, for the first time, a synergistic interaction of continuously administered opioid and local anesthetic during visceral antinociception.

Some clinical reports have shown enhanced analgesia after the administration of opioids or local anesthetics,[1,2,10] whereas others have failed to show potentiated analgesia compared with each drug alone.[13–15] The appearance of greater analgesic effects with coinfusion in stressful conditions, such as coughing or deep breathing,[33] suggests the presence of at least additive analgesic levels during the infusion of those combinations. Those differences in results may be attributed to the difficulty in quantifying analgesic effects in patients with dynamic pain states, to the different doses necessary to provide satisfactory pain relief, or both. Recently, Brennum *et al.*[34] quantitatively evaluated the effects on nociceptive and nonnociceptive somatosensory functions of epidural combination of morphine and bupivacaine in healthy volunteers. They showed that the combination had lesser peak effects but a more prolonged hypoalgesic

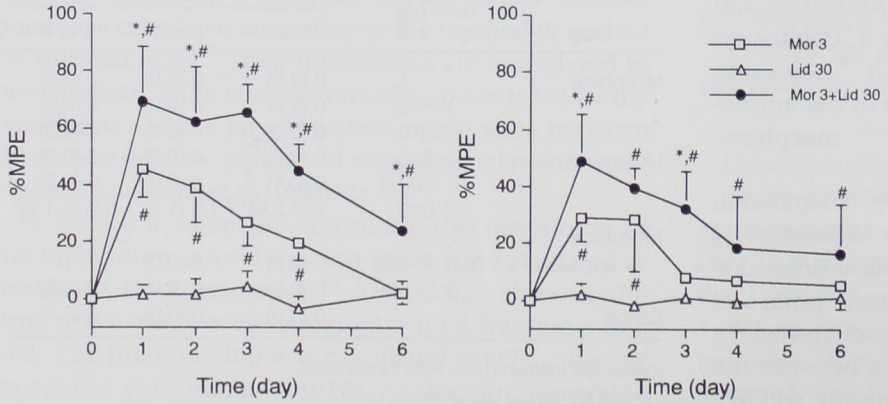

Fig. 4. The time course of effects on percentage maximum possible effect in the tail flick test (*left*) and the colorectal distension test (*right*) during intrathecal infusion of morphine (Mor) at 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 7), lidocaine (Lid) at 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 6), or the combination of those (n = 6) for 6 days. Data are presented as the mean ± SD. *Significantly different from 0.3 Mor. #Significantly different from 30 Lid.

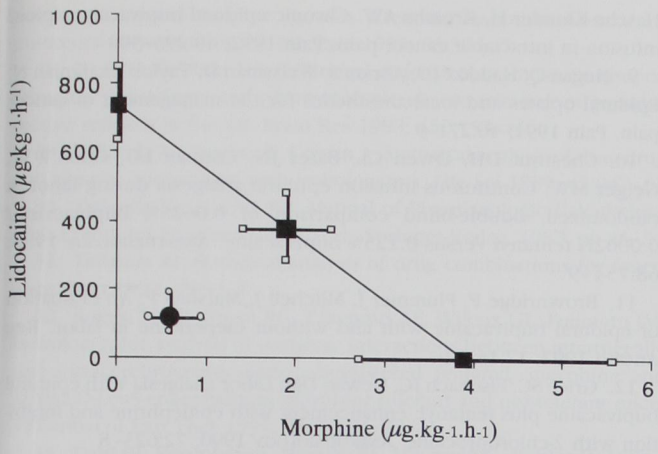

Fig. 5. An isobologram of antinociceptive median effective dose (ED_{50}) values and 95% confidence intervals (CIs) for morphine (horizontal), lidocaine (vertical) or a combination of morphine and lidocaine (point in the dose field). The heavy lines represent the CIs. The dashed diagonal line connecting the morphine and lidocaine ED_{50} values (closed square on the axes) are the theoretical additive line, and the point on this line (large closed square) is the theoretical additive point. The fact that the experimental points (closed circle) evaluated fell below the theoretical additive points indicates that the antinociceptive effects produced by the combination were synergistic.

action than bupivacaine alone, and it induced a faster onset and had a modest increase in hypoalgesic effect, even beyond the duration of bupivacaine when administered alone. Those findings agree with our results, which show that the intrathecal coinfusion of morphine and lidocaine potentiated the duration and the magnitude of their own antinociceptive effects. The results of this study proved that coinfusion of opioids and local anesthetics strongly potentiated their analgesic effects and agree with the rationale for coinfusing opioids and local anesthetics in the clinical setting.

Our study revealed a differential time course of effects between somatic and visceral antinociception with the continuous infusion of morphine or lidocaine alone. The increases in %MPE in the TF test from day 1 through day 3 after morphine infusion was much greater than those in the CD test, suggesting a greater somatic antinociceptive effect, although such a precise comparison is difficult because of the different characteristics of the two tests. However, in contrast to this study, when a bolus of morphine or lidocaine was injected *via* the epidural[16] or intrathecal route (results from morphine challenge after the saline infusion group in part II) only minor differences in time-course effects between the TF and CD tests were observed.

Differences in the time course of antinociceptive effects may be, in part, attributed to the small dose and volume used in continuous infusions when compared with bolus injection. Because of anatomic features of visceral afferent pathways,[22,23,35] such as wide divergence in the spinal cord or sparse innervation of visceral afferent to the spinal cord, visceral antinociception may be influenced more strongly by the dose and volume of administered drugs than is somatic antinociception. A continuous infusion (smaller volume and dose) may cause less visceral antinociception, whereas the large dose and volume of a bolus injection may have a greater effect on visceral antinociception, because colorectal distension widely activates spinal dorsal horn neurons from lower thoracic segments to lumbosacral segments.[36,37] This could explain the apparent difference in the observed visceral antinociception between a bolus injection and a continuous infusion. In support of this are our observations that visceral, but not somatic, antinociception during intrathecal infusion of morphine are enhanced when the infused volume of morphine is increased with the same total dose.[38] Those results agree with the concept that visceral antinociception depends more on the expansion of morphine solution than does somatic antinociception at the spinal cord, and the localized expansion of morphine presumably results in the reduced suppression of visceral afferent input in many spinal segments.

Despite the small dose, synergistic interaction on visceral and somatic antinociception was clearly shown in this study. Coadministration of morphine and lidocaine dramatically improved the antinociceptive effects, especially visceral antinociception, which was not shown after infusion of either drug alone. That is very important in taking care of pain originating from viscera in clinical practice, because components of postoperative and cancer-related pain are of visceral origin.[20]

We did not evaluate combined doses to produce 100 %MPE. Because our main focus was to determine whether combinations of morphine and lidocaine produce a synergistic antinociception, we used small doses. It may be necessary in the clinical setting to use higher doses to provide complete analgesia. However, our results agree with the hypothesis that such a combination would produce synergy and cause reduction of infused dose, resulting in a low incidence of adverse side effects associated with each drug.

We used morphine, a μ-receptor agonist, and lidocaine to evaluate the antinociceptive interaction of opioid and local anesthetics at the spinal level because they are popular in clinical practice and many comparable data have been cumulated in previous studies. However, the

nature of the interaction may be altered depending on the type of opioid receptor subtype or local anesthetic. Different opioid receptor subtypes have different characteristics and demonstrate different antinociceptive effects.[25,39–41] Individual local anesthetics have different features, such as potency, duration, and motor block. Visceral antinociceptive effects and potency at the spinal level also vary in association with the opioid subtype.[25,27] Therefore, many combinations of opioids and local anesthetic are possible, and it is important to determine an optimal combination considering the characteristics of pain and the drugs to be administered. This study cannot answer all questions, but it is a first step in showing the synergistic antinociception of the drugs on somatic and visceral pain in long-term use. More studies are needed to elucidate the antinociceptive interaction of different drug combinations, the timing of their administration, and different dose ratios for the combined drugs.

Intrathecally coadministered morphine and lidocaine synergistically potentiated the magnitude and duration of antinociceptive effects on somatic and visceral stimuli. Such synergistic combinations may provide an important tool to control clinical pain.

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