

Anesthesiology
80:137-150, 1994
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Synergistic Antinociceptive Interaction after Epidural Coadministration of Morphine and Lidocaine in Rats

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Background: Clinically, epidural coadministration of opioids and local anesthetics has provided excellent analgesia for various types of pain. However, information about the interaction of these drugs when administered epidurally is limited. Therefore, we evaluated the antinociceptive interaction between morphine and lidocaine on both somatic and visceral noxious stimuli in the rat.

Methods: Male Sprague-Dawley rats weighing 300–350 g had epidural catheters implanted at T13–L1. Every rat was tested with both the tail flick test, a somatic noxious stimulus, and the colorectal distension test, a visceral noxious stimulus. In the colorectal distension test, the response threshold was defined by the pressure within the intracolonic balloon required to trigger abdominal contraction. Tail flick latency and colorectal distension threshold were measured before and for 180 min after the administration of morphine, lidocaine, or combinations of those drugs. To characterize the interaction, isobolographic analysis was performed with a fixed morphine: lidocaine dose ratio of 1:1,000.

Results: Epidural morphine (0.1–10 µg) and lidocaine (100–800 µg) increased the tail flick latency and colorectal distension threshold in a dose- and time-dependent fashion. The epidural injection of morphine (0.1–1 µg) mixed with lidocaine (100 or 200 µg) significantly increased the peak effect and pro-

longed the duration of effects compared with each drug alone in both nociceptive tests. Areas under the curves, calculated to express overall magnitude and duration of antinociceptive effects, were significantly increased by combinations as compared with each drug alone, especially with morphine 0.1 µg and lidocaine 100 or 200 µg, each of which alone produced no change in the area under the curve. Isobolographic analysis revealed that epidural morphine and lidocaine interact synergistically at 10, 20, and 30 min after injection in both somatic and visceral nociception tests. Both potency ratio analysis and fractional analysis confirmed the finding of the isobolographic analysis. Epidural naloxone antagonized the antinociceptive effects produced by the combination.

Conclusion: These data demonstrate that epidurally administered morphine and lidocaine produce synergistic analgesia and prolong the duration of analgesia in tests of somatic and of visceral nociception. (Key words: Analgesics, opioid: morphine. Anesthetic techniques: epidural. Anesthetics, local: lidocaine. Interactions (drug): synergy. Pain: somatic; visceral.)

MANY clinical studies have shown that the combination of a local anesthetic and an opioid produces excellent analgesia in postoperative,¹⁻⁷ labor,⁸⁻¹¹ and cancer-related pain.¹²⁻¹⁴ The objective of the combination therapy is to reduce the amount of each drug and thereby minimize the incidence and severity of side effects. The combination of an epidural local anesthetic and an opioid has improved pain relief compared with epidural local anesthetic alone after abdominal,¹⁻³ thoracic,⁴ and gynecologic^{5,6} surgery and in labor.⁸⁻¹¹ In contrast, results from studies comparing epidural opioid and local anesthetic mixtures with epidural opioid alone are conflicting.^{1,4,5,15-17} Most studies report a greater analgesia with epidural combination than with epidural opioid alone, but statistically significant benefits have rarely been observed. Although many investigators have postulated a synergistic analgesic interaction between epidural or intrathecal opioids and local anesthetics, there is no clinical evidence to prove such an effect. This interaction would be difficult to elucidate clinically because administration of ineffec-

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Received from the Department of Anesthesiology, Shimane Medical University, Izumo, Japan, and the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication August 28, 1993. Presented in part at the annual meeting of the Society for Neuroscience, New Orleans, Louisiana, November 1991.

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tive analgesic doses of each drug has practical and ethical problems.

Recently, several studies have demonstrated synergistic antinociceptive interactions between opioids and local anesthetics in mice¹⁸ or rats^{19,20} when the drugs were administered intrathecally. Clinically, epidural administration of drugs is a more popular method than intrathecal administration. Epidurally administered opioids or local anesthetics have more complicated mechanisms with regard to sites of action and pharmacokinetics than do those administered intrathecally.^{21,22}

The purpose of this study was to evaluate antinociceptive interactions between epidurally coadministered morphine and lidocaine on both somatic and visceral nociceptive tests and to use isobolographic analyses to determine if the interactions are synergistic.

Materials and Methods

The protocol for this experiment was approved by the Animal Research and Use Committee of Shimane Medical University. Male Sprague-Dawley rats (Clea, Japan) weighing 300–350 g were maintained on a 12-h light–dark schedule and were housed individually with free access to food and water.

Animal Preparation and Surgical Procedure

To reduce the influence of handling on nociceptive responses, all animals were handled and trained in the test situation for at least 5 days before epidural catheterization. For epidural catheterization, anesthesia was induced by placing the rat in a closed box containing 4% halothane in oxygen. After loss of consciousness, anesthesia was maintained with 2% halothane *via* a loose-fitting plastic mask. The skin of the back was shaved in the thoracolumbar region, and 10% povidone iodine applied. To flex the lower thoracic and lumbar vertebral column during surgery, a foam block was placed under the animal's abdomen. The last ribs were palpated to identify the T13 vertebra. A midline skin incision was made over the spinous processes of the T12 and L2 vertebrae. The fascia was opened, and superficial muscles around the spinous process were dissected and retracted laterally. With the use of fine forceps, the ligament was pierced. The catheter was made of two polyethylene tubes, 1.5-cm-long PE-10 (ID 0.28 mm, OD 0.61 mm) and 15-cm-long PE-20 (ID 0.38 mm, OD 1.09 mm), which were heat-sealed together.

The PE-10 part was gently introduced caudally into the lumbar epidural space. A drop of surgical glue (α cyanoacrylate, Aron-Alpha, Toagosei, Tokyo) was applied over the site of entry of the catheter to the epidural space. The remainder of the catheter was tunneled subcutaneously and exteriorized through the skin in the neck region. Cefazolin sodium 50 mg was injected intramuscularly, and the skin incision was closed.

Rats exhibiting any neurologic deficits, infection, or other health problems after surgery were excluded from this experiment ($n = 5$). After surgery, rats were allowed to recover for 4 days before experimentation. Location of the distal end of the catheter was verified at the end of an experiment by injection of indigo carmine and *post mortem* examination of the spinal cord. Data obtained from animals in which the dye failed to stain the lumbar epidural space or in which the spinal cord had observable damage were not included in the data analysis ($n = 17$). Data from 62 animals were included in data analysis.

Nociceptive Tests

The individual performing the nociceptive test and motor function test was blinded to the drug injected.

Tail Flick Test. The tail flick (TF) test was performed to measure the response to a noxious somatic stimulus. The time between stimulus onset and withdrawal of the tail from the heat source (a 50-W projector lamp) focused on a distal segment of the tail (approximately 5 cm from the tip) was defined as the response latency. The apparatus (model DS20, Ugo Basile, Comerio-Varese, Italy) was calibrated to give an average baseline latency of about 4 s. A cut-off latency of 10 s was used to prevent tissue damage.

Colorectal Distension Test. To assess visceral nociception, the colorectal distension (CD) test modified from Ness and Gebhart²³ was performed. This test consists of air inflation of a 8-cm-long flexible latex balloon that consists of two parts, a stimulating balloon and sensing balloon. Pressure within each part was monitored continuously *via* in-line pressure transducers and recorded (Rectigraph, Sanei, Japan). The balloon was inserted intraanally into the descending colon and rectum under light halothane anesthesia. Animals were tested while awake after recovery from anesthesia. Pressure within the stimulating balloon was steadily increased at a rate of 2.5 mmHg/s beginning at 0 mmHg and until the abdominal musculature contracted and repeated, rapid increase of the pressure (spikelike

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waves) in the sensing balloon was detected. The minimal pressure at which abdominal contractions were triggered was defined as the threshold for visceral nociception in this test. A cut-off distension pressure of 60 mmHg was used to prevent tissue damage.

Motor Function Test

Motor function after epidural injection was assessed by bilaterally grading the motor block in the lower limbs as follows: 0 = none; 1 = partially blocked; and 2 = completely blocked. Motor blockade was graded as none when the rat had no visible limb weakness and normal gait; as partially blocked when the limb was able to move but not able to support the normal posture; and as completely blocked when the limb was flaccid, with no detectable resistance to extension of the limbs. The normal baseline score was 0, and the score with bilateral complete blockade was $2 \times 2 = 4$. The score was reassessed immediately after every nociception test.

Measurements

On the day of an experiment, the CD balloon was inserted during light halothane anesthesia, and the rat was allowed to recover from the halothane at least for 20 min before determination of baseline values for both the TF and the CD test. Both TF and CD tests were performed in each rat at the same time points, with 2-min intervals between each test. Each animal was tested on multiple days (not more than 3) but never received the same dose of drug twice, and each recovered for 2 days between experimental tests.

After determination of the baseline values, one of the following regimens was administered by single bolus epidural injection:

1. Lidocaine hydrochloride: 100 μg ($n = 9$), 200 μg ($n = 9$), 400 μg ($n = 7$), or 800 μg ($n = 8$)
2. Morphine hydrochloride: 0.1 μg ($n = 10$), 1 μg ($n = 10$), or 10 μg ($n = 10$)
3. Combination: morphine 0.1 μg + lidocaine 100 μg ($n = 8$), morphine 0.1 μg + lidocaine 200 μg ($n = 8$), morphine 1 μg + lidocaine 100 μg ($n = 8$), or morphine 1 μg + lidocaine 200 μg ($n = 10$)
4. Normal saline ($n = 5$).

All drug injections were given in a volume of 40 μl administered manually over 30 s, followed by a 15- μl flush of normal saline. TF latency and CD threshold were measured at 5, 10, 15, 20, 30, 60, 90, 120, and

180 min after injection of morphine alone or the combination and for 90 min after lidocaine alone.

To construct dose-effect curves, additional data were obtained for morphine or lidocaine alone and in combination. Additional morphine doses were 0.2 μg ($n = 6$) and 3 μg ($n = 6$), and additional lidocaine doses were 50 μg ($n = 6$), 600 μg ($n = 7$), and 2,000 μg ($n = 6$). To perform isobolographic analysis, the dose ratio of the combination was fixed at morphine:lidocaine = 1:1,000. The doses for additional data were morphine 0.05 μg + lidocaine 50 μg ($n = 8$), morphine 0.2 μg + lidocaine 200 μg ($n = 8$), and morphine 0.4 μg + lidocaine 400 μg ($n = 8$).

To assess opioid antagonism, some animals received 10 μg naloxone epidurally 10 min before ($n = 8$) or 10 min after ($n = 6$) the injection of the morphine-lidocaine combination, and measurements were repeated for 180 min in the same way.

Statistical Analysis

TF latency and CD threshold were converted to percent maximum possible effect (MPE): %MPE = (post-drug value - baseline value) / (cut-off value - baseline value) \times 100%. Area under the time-effect curve (AUC) was calculated by accumulating the effect (%MPE) measured at the discrete time intervals using the trapezoidal integration method. %MPE and AUC are presented as means \pm SEM. Changes in %MPE after epidural injection were analyzed using two-way analysis of variance for repeated measures to assess the influence of treatment and time, followed by Scheffé's *post hoc* test for between-group comparison and by a paired *t* test for within-group comparison. Differences in AUC between groups were analyzed by one-way analysis of variance and Scheffé's test for *post hoc* comparison. To analyze the motor function after epidural injection, the individual motor block scores for each rat were cumulated, and the comparison between treatment groups was accomplished by testing Kruskal-Wallis analysis of variance by ranks. Individual comparisons were carried out with the Mann-Whitney U test. A *P* value < 0.05 was considered to be statistically significant.

Isobolographic Analysis

To determine whether the antinociceptive interaction of morphine and lidocaine are additive or synergistic, isobolographic analysis was performed by method of Tallarida *et al.*²⁴ First, three dose-effect curves were determined: two with morphine or lidocaine given alone and a third with a combination of morphine and

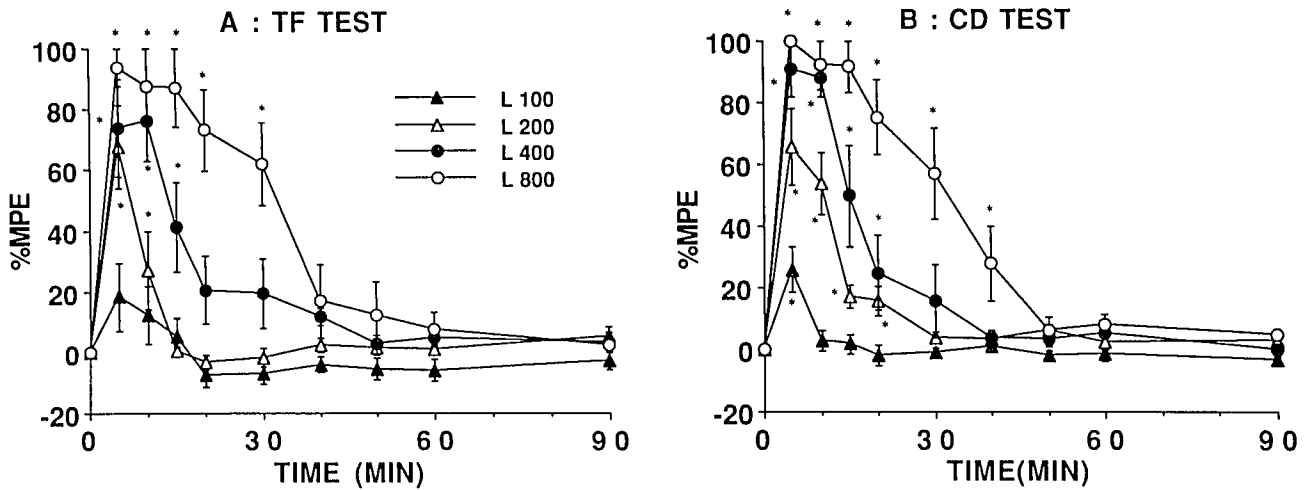


Fig. 1. Time-course effects on percent maximum possible effect (%MPE) in the tail flick (TF) test (A) and colorectal distension (CD) test (B) after epidural administration of lidocaine (L) 100, 200, 400, and 800 μg ; $n = 7-9$ for each group. Data are presented as means \pm SEM. *Significantly different from baseline value.

lidocaine at a fixed dose ratio. Four or five points ($n = 6-10$ for each) were used to determine each dose-effect curve. The construction of the dose-effect curves and the determination of doses producing 50% MPE (ED_{50}) as well as 95% confidence intervals (CIs) were computed.²⁵ The resulting ED_{50} values were then 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 CI for the combination was placed in the dose field. The theoretical additive line is presented 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.*²⁴ (See fig. 7.) Drug interactions were considered to be synergistic if the combination ED_{50} point was below the theoretical additive line. Statistical significance between theoretical additive points and experimental points was evaluated according to Tallarida.²⁶

To obtain a value for describing the magnitude of the interaction, a total fraction value was calculated as described by Roerig *et al.*²⁷ The ED_{50} values of the drug given alone were assigned the number 1. Then, total fraction = (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 indicates an additive interaction, and values less than 1 implied a supraadditive interaction.

Potency ratio analysis was used to compare the experimental combination ED_{50} with the theoretically

additive ED_{50} . Here, potency ratio = (experimental ED_{50} for the combination)/(theoretical ED_{50} for the combination). The CIs of the potency ratio were calculated by the method of Lichfield and Wilcoxon.²⁸ When the lower limit of the CI is greater than 1, the ratio is significant.

Results

Effect of Epidural Lidocaine

Lidocaine given epidurally produced dose- and time-dependent antinociceptive effects in both the TF and CD tests (fig. 1). The peak effects were observed at 5 min after drug administration. Lidocaine 50 μg produced no significant change in either test (data not shown in fig. 1), and lidocaine 100 μg produced a minimal increase in TF latency and CD threshold that was significant only for the CD test at 5 min after administration. Time-effect curves for each dose of lidocaine were almost comparable between the TF and CD tests. With the 200- and 800- μg doses, the durations of significant increase in %MPE were slightly longer in the CD test (20 and 40 min, respectively) than in the TF test (10 and 30 min, respectively).

Motor block scores for lidocaine are shown in table 1. Significant motor impairment was not observed with lidocaine 100 μg or less. Lidocaine 200 μg produced partial block at 5 min (mean block score 1.6) and 10 min (1.2) after injection. After administration of li-

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Table 1. Motor Block Score after Epidural Injection of Lidocaine Alone and in Combination with Morphine

Drug Dose (μg)		Score		
Lidocaine	Morphine	Lidocaine Alone	Combination	
50	0.05	0 (0)	0 (0)	NS
100	0.1	0.9 (0.5)	0.8 (0.3)	NS
	1.0		0.9 (0.4)	NS
200	0.1		2.7 (0.5)	NS
	0.2	2.9 (0.4)	2.4 (0.7)	NS
	1.0		3.0 (0.5)	NS
400	0.4	6.1 (1.1)	6.3 (1.0)	NS
800	—	12.1 (1.2)	—	
2,000	—	20.1 (1.3)	—	

Values are the mean (with SEM in parentheses) of the cumulative motor block score.

NS = not significant.

lidocaine 400 μg , complete hindlimb paralysis was observed in four of seven animals and partial block in three at 5 min, with full recovery at 15 min in four animals and at 20 min in three. Lidocaine 800 and 2,000 μg produced complete paralysis lasting for 10 and 30 min, respectively, with full recovery observed at 30 min and 50 min, respectively.

Effect of Epidural Morphine

Antinociceptive effects of epidurally administered morphine (0.1–10 μg) were dose- and time-dependent in both the TF and CD tests, with a slightly later onset and a much longer duration than with epidural lidocaine (fig. 2). Morphine 0.1 μg produced a small but

significant increase in TF latency at 5, 10, and 15 min. In the CD test, however, morphine 0.1 μg produced no significant effect. In both tests morphine 1 and 10 μg produced significant effects within the first 5 min after epidural administration. The peak effect occurred more rapidly with 10 μg morphine (10 min) than with smaller doses (15 min). At 180 min after administration of 10 μg morphine, TF latency and CD threshold were still increased to 73 and 53 %MPE, respectively, compared with baseline values.

None of the morphine doses tested produced any evidence of motor impairment. Epidural administration of normal saline produced no significant change in either somatic or visceral nociceptive responses (fig. 2) and no evidence of motor impairment.

Effect of Combined Epidural Morphine and Lidocaine

Coadministration of lidocaine 100 or 200 μg and morphine 0.1 or 1 μg significantly increased %MPE compared with both the same dose of morphine alone and lidocaine alone in both the TF and the CD tests (fig. 3). The augmentation effect of the addition of lidocaine 100 μg to morphine 1 μg was observed at early time points (5 and 10 min) in both the TF and the CD tests and even at later time points (90 and 120 min) in the CD test. Combination of lidocaine 200 μg , which had no effect at and after 30 min, with morphine 1 μg produced significantly greater effects in both the TF and the CD tests. These effects lasted 120 min, unlike both the same dose of morphine alone and the same dose of lidocaine alone, except for the 5-min time

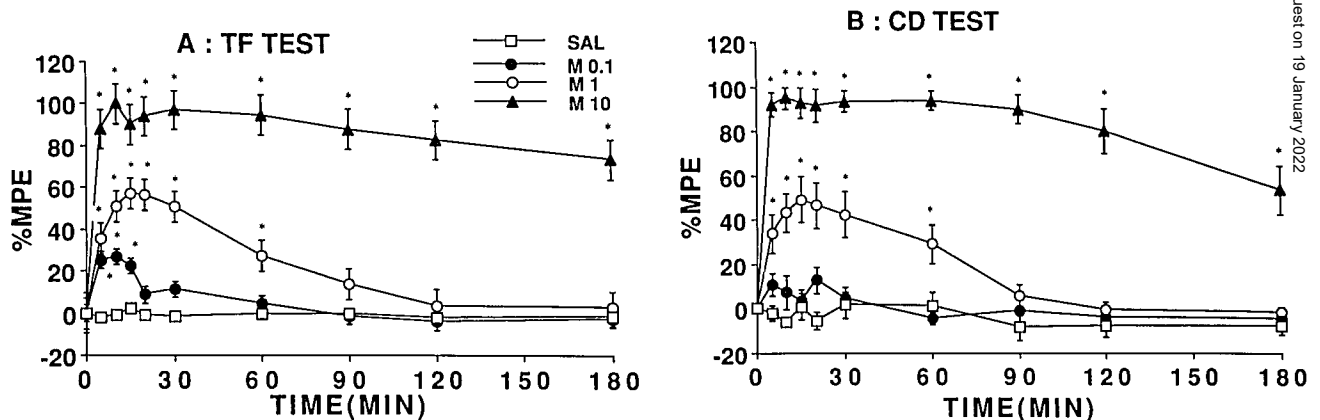


Fig. 2. Time-course effects on percent maximum possible effect (%MPE) in the tail flick (TF) test (A) and colorectal distension (CD) test (B) after epidural administration of saline (SAL) or morphine (M) 0.1, 1, and 10 μg ; $n = 5$ for the saline group and 10 for each morphine group. Data are presented as mean \pm SEM. *Significantly different from baseline value.

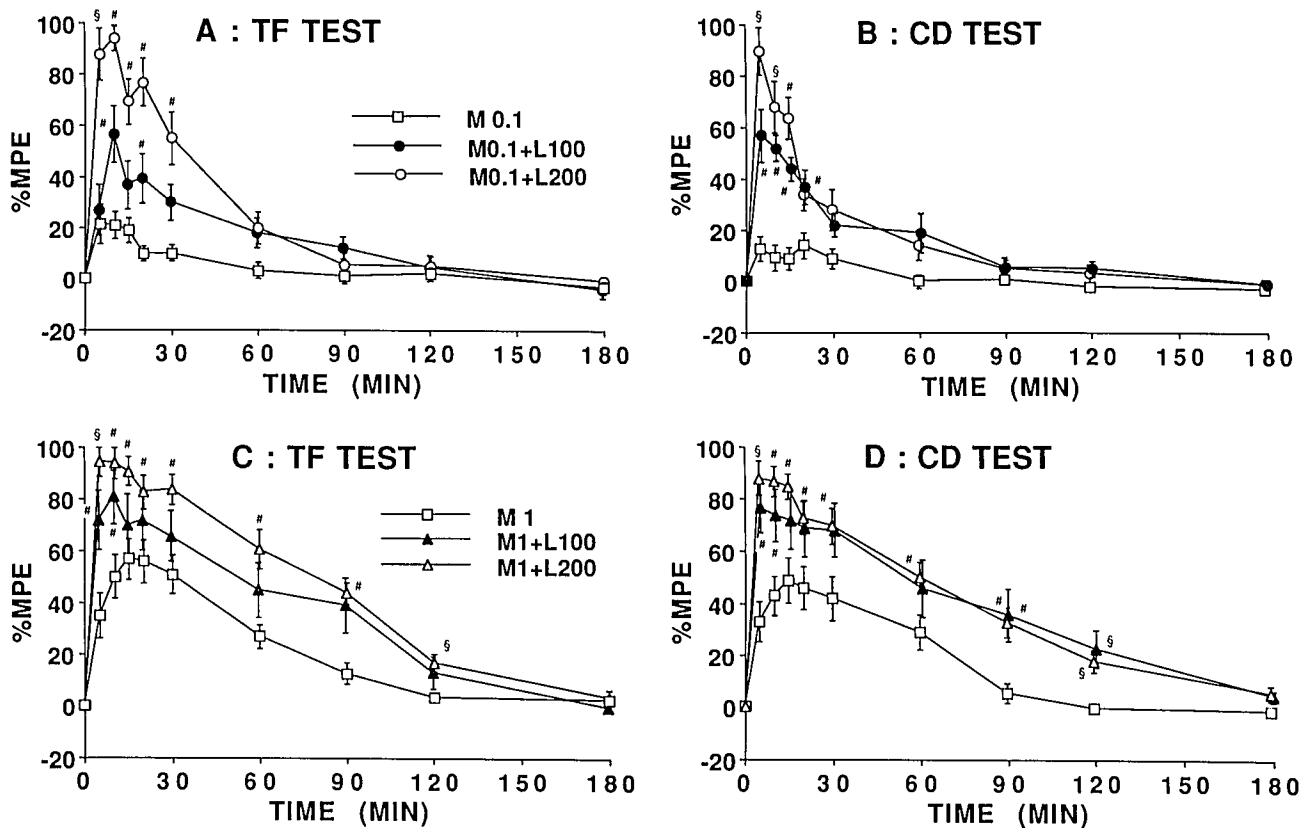


Fig. 3. Time-course effects on percent maximum possible effect (%MPE) in the tail flick (TF) test (A, C) and colorectal distension (CD) test (B, D) after epidural coadministration of morphine (M) and lidocaine (L). Groups are morphine 0.1 μg + lidocaine 100 μg ($n = 8$), morphine 0.1 μg + lidocaine 200 μg ($n = 8$), morphine 1 μg + lidocaine 100 μg ($n = 8$), and morphine 1 μg + lidocaine 200 μg ($n = 10$). Data for morphine alone are transferred from figure 2. Data are presented as means \pm SEM. §Significantly different compared with the same dose of morphine alone at individual time points; #significantly different compared with both the same dose of morphine alone and lidocaine alone at individual time points.

point, when this dose of lidocaine alone had significant effects (figs. 3C and 3D). Coadministration of morphine 0.1 μg and lidocaine 100 μg —which, by itself, had no or only minimal effect in the TF and the CD tests—increased the %MPE for 20 min in the CD test and at 10 and 20 min in the TF test (figs. 3A and 3B), by much more than by simple addition of the effects produced by morphine alone and lidocaine alone.

Coadministration of morphine 0.1 μg with lidocaine 100 or 200 μg , none of which alone had a significant effect on AUC, significantly increased AUCs in both the TF and the CD tests ($P < 0.01$) (fig. 4). Morphine 1 μg alone produced a significant increase in the AUC in both the TF and the CD tests, and addition of lidocaine 100 or 200 μg resulted in an almost 2.5-fold increase in AUCs in both tests.

Combination of morphine and lidocaine resulted in no increase of motor impairment as indicated by the cumulative motor block score. Statistically significant differences in the score were not observed in any combination groups compared with the same dose of lidocaine alone (table 1).

Effect of Naloxone

Epidural injection of 10 μg naloxone, after a peak effect had been obtained by coadministration of morphine 1 μg and lidocaine 100 or 200 μg , resulted in an immediate return to baseline level for both the TF latency and the CD threshold (fig. 5). Epidural pretreatment with 10 μg naloxone antagonized the effects to be produced by coadministered morphine 1 μg and lidocaine 200 μg (fig. 6). At 5 min after the injection

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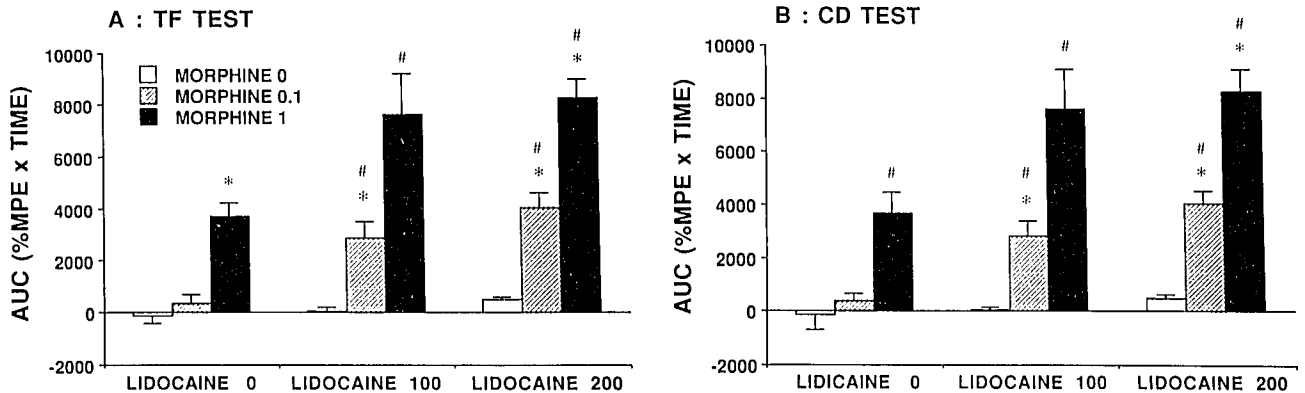


Fig. 4. Histogram showing the area under the curve (AUC) for 0.1 or 1 µg of morphine alone, 100 or 200 µg of lidocaine alone, and their combinations in the tail flick (TF) test (A) and colorectal distension (CD) test (B). AUCs were calculated from time-effect curves of each rat for 90 min (lidocaine group) or for 180 min (morphine group and combination group) after injection of drugs. MPE = maximum possible effect. Data are presented as means \pm SEM; $n = 5-10$ for each group. *Significantly different compared with the same dose of morphine alone; #significantly different compared with the same dose of lidocaine alone.

of the morphine-lidocaine combination, there was a moderate increase in %MPE that was significant in the CD test but not in the TF test. The time-effect curves for the combination with naloxone pretreatment were almost comparable to those for the same dose of lidocaine alone, with regard to the onset and magnitude of peak effect and the duration of action.

Isobolographic Analysis

The ED_{50} values and CIs for morphine, lidocaine, and the combination at 10, 20, and 30 min after administration in each test are summarized in table 2. The ex-

perimentally derived ED_{50} value and CI in the TF test at 10 min plotted in the TF isobologram fell below the theoretical dose-additivity line, and the CIs of the theoretical additive point and those of the experimental point did not overlap with each other (fig. 7A). 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 at 10 min after epidural administration in the TF test. As illustrated in figures 7B and 7C, morphine and lidocaine also clearly showed synergistic interaction in the TF test at both

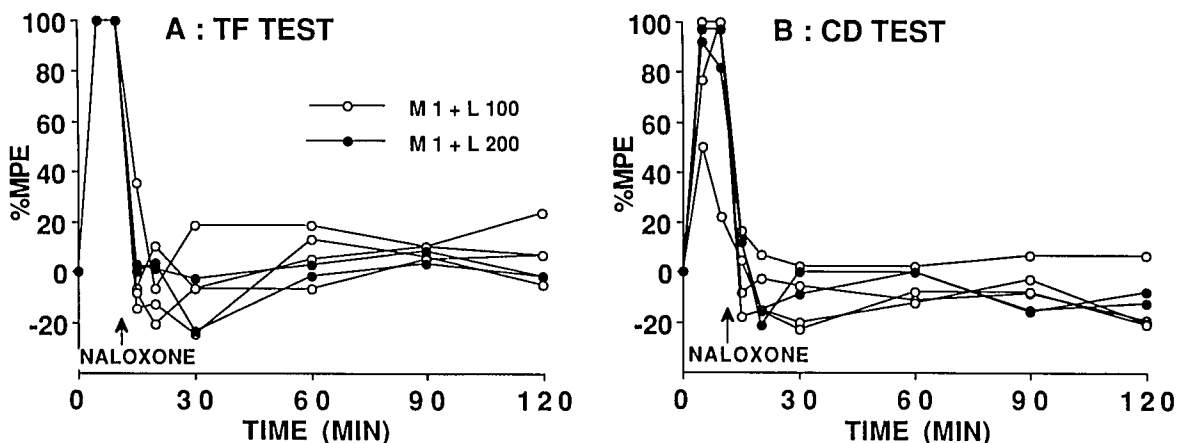


Fig. 5. Effects of epidurally administered naloxone on antinociception of the epidural morphine (M)-lidocaine (L) combination in the tail flick (TF) test (A) and colorectal distension (CD) test (B). The epidural injection of naloxone (10 µg), after a maximal effect had been obtained by the coadministration of morphine and lidocaine, rapidly abolished the antinociceptive effect in both the TF and CD tests. MPE = maximum possible effect. Data for each rat are presented.

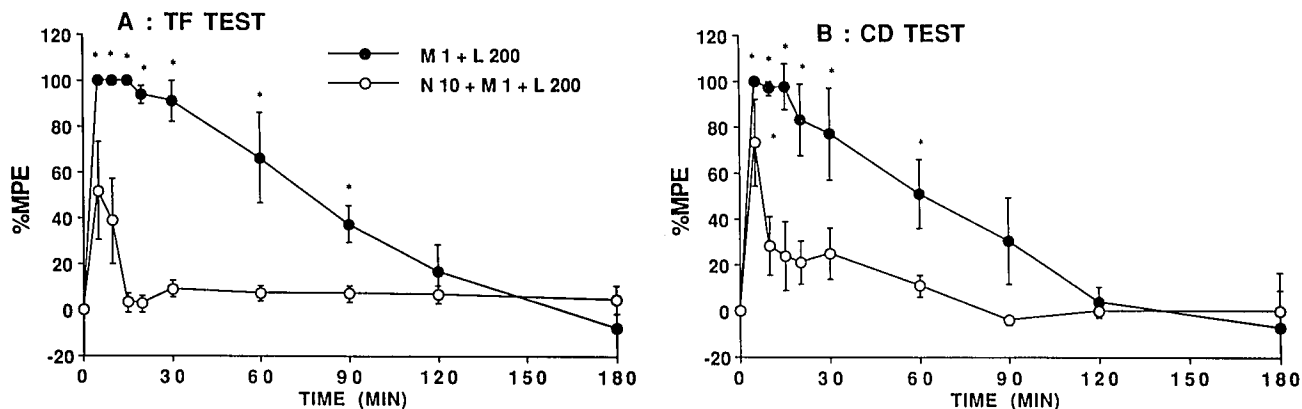


Fig. 6. Effects of pretreatment with epidural naloxone (N) on the time-course effects of the epidural morphine (M)-lidocaine (L) combination in the tail flick (TF) test (A) and colorectal distension (CD) test (B). Doses are morphine 1 μ g, lidocaine 200 μ g, and naloxone 10 μ g. MPE = maximum possible effect. Data are presented as mean \pm SEM; $n = 8$ for each group. *Significantly different from baseline value.

20 and 30 min after injection ($P < 0.05$). Isobolographic analysis for the CD test, at 10, 20, and 30 min after administration, also showed synergistic interaction between morphine and lidocaine (figs. 7D, 7E, and 7F) ($P < 0.05$).

To evaluate the potentiation effect resulting from the interaction between morphine and lidocaine, potency ratios were calculated from experimental ED_{50} values for combination and theoretically additive ED_{50} values (table 2). Potency ratios exceeded 1.0 at all time points in both the TF and the CD tests, with the lower limit of each CI being greater than 1, indicating that these potency ratio values are statistically significant.

To compare the magnitude of the effectiveness of the combination in reducing the total dose required to

produce a given effect, the total fractions were calculated (table 2). Total fraction values calculated from ED_{50} values presented in table 2 were less than 1 at all time points in both the TF and the CD tests, also indicating synergistic interaction. A low total fraction indicates that only a low-dose combination is needed to produce a specific effect.

These results, both those according to calculation of potency ratios and those according to total fractions, duplicated those of isobolographic analysis.

Discussion

The results of the current study clearly demonstrate that epidurally coadministered morphine and lidocaine

Table 2. ED_{50} Values and 95% Confidence Intervals after Epidural Morphine, Lidocaine, and Morphine-Lidocaine Combination

Test	Time (min)	Morphine	Lidocaine	Combination*	Morphine/Lidocaine Doses (μ g) in Combination	Potency Ratio†	Total Fraction
Tail flick	10	1.50 (1.17-1.93)	355 (298-425)	107.7 (94.3-123.0)	0.11/107.59	2.6 (2.0-3.4)	0.38
	20	1.14 (0.96-1.35)	1,020 (933-1,116)	177.9 (155.1-204.0)	0.18/177.72	3.0 (2.3-3.8)	0.33
	30	1.45 (1.08-1.95)	1,065 (926-1,225)	194.7 (154.7-245.2)	0.19/194.51	3.2 (2.1-4.7)	0.32
Colorectal distension	10	2.05 (1.60-2.63)	317 (253-395)	102.0 (79.1-127.3)	0.10/101.90	2.7 (1.9-3.7)	0.37
	20	1.31 (0.98-1.72)	875 (778-985)	177.9 (136.2-232.7)	0.17/177.73	2.9 (2.0-4.3)	0.34
	30	1.80 (1.35-2.38)	1,046 (1,046-1,356)	208.4 (172.7-250.9)	0.21/208.19	3.2 (2.1-4.8)	0.32

Values are the ED_{50} (and 95% confidence interval in parentheses) (micrograms).

* The dose ratio of the combination was morphine to lidocaine at 1:1,000.

† The potency ratio is calculated from the experimental combination ED_{50} (presented in the table) and the theoretically additive ED_{50} (not shown in the table), and its confidence interval is given in parentheses.

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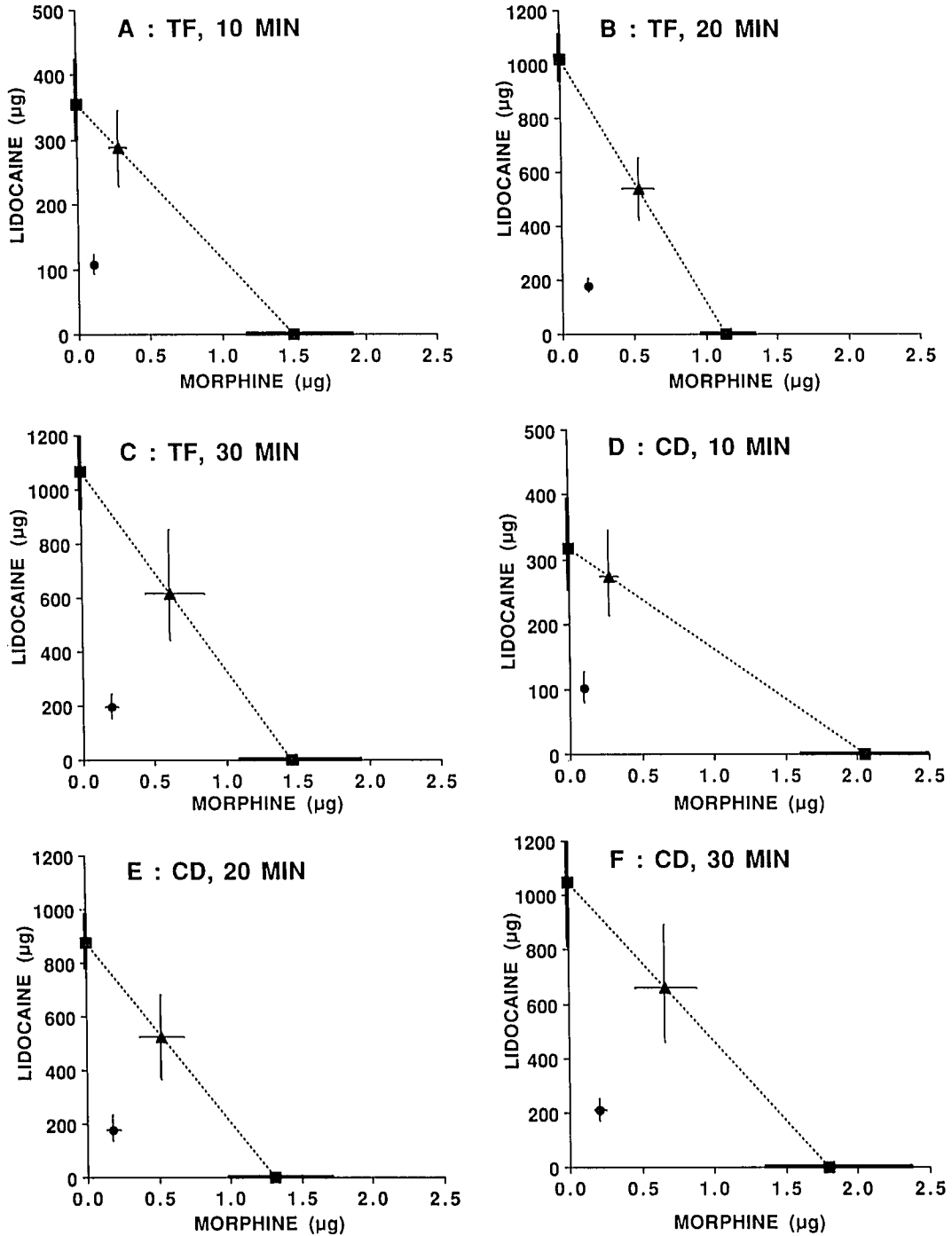


Fig. 7. Isobologram of antinociceptive ED₅₀ (dose producing 50 %MPE) values and 95% confidence intervals for morphine (square on the horizontal axis), lidocaine (square on the vertical axis), or the morphine-lidocaine combination (circle in the dose field) at 10, 20, and 30 min after epidural injection in the tail flick (TF) test (A-C) and colorectal distension (CD) test (D-F). The heavy lines on the axes represent the confidence intervals for the single agents. The dashed diagonal line connecting the morphine and lidocaine ED₅₀ values (closed square on the axes) is the theoretical additive line, and the point on this line (triangle) is the theoretical additive point (and confidence interval). The fact that the experimental points (and confidence intervals) in both tests at all time points evaluated fell below the theoretical additive points (and confidence intervals) indicates that the antinociceptive effects produced by the combination were synergistic.

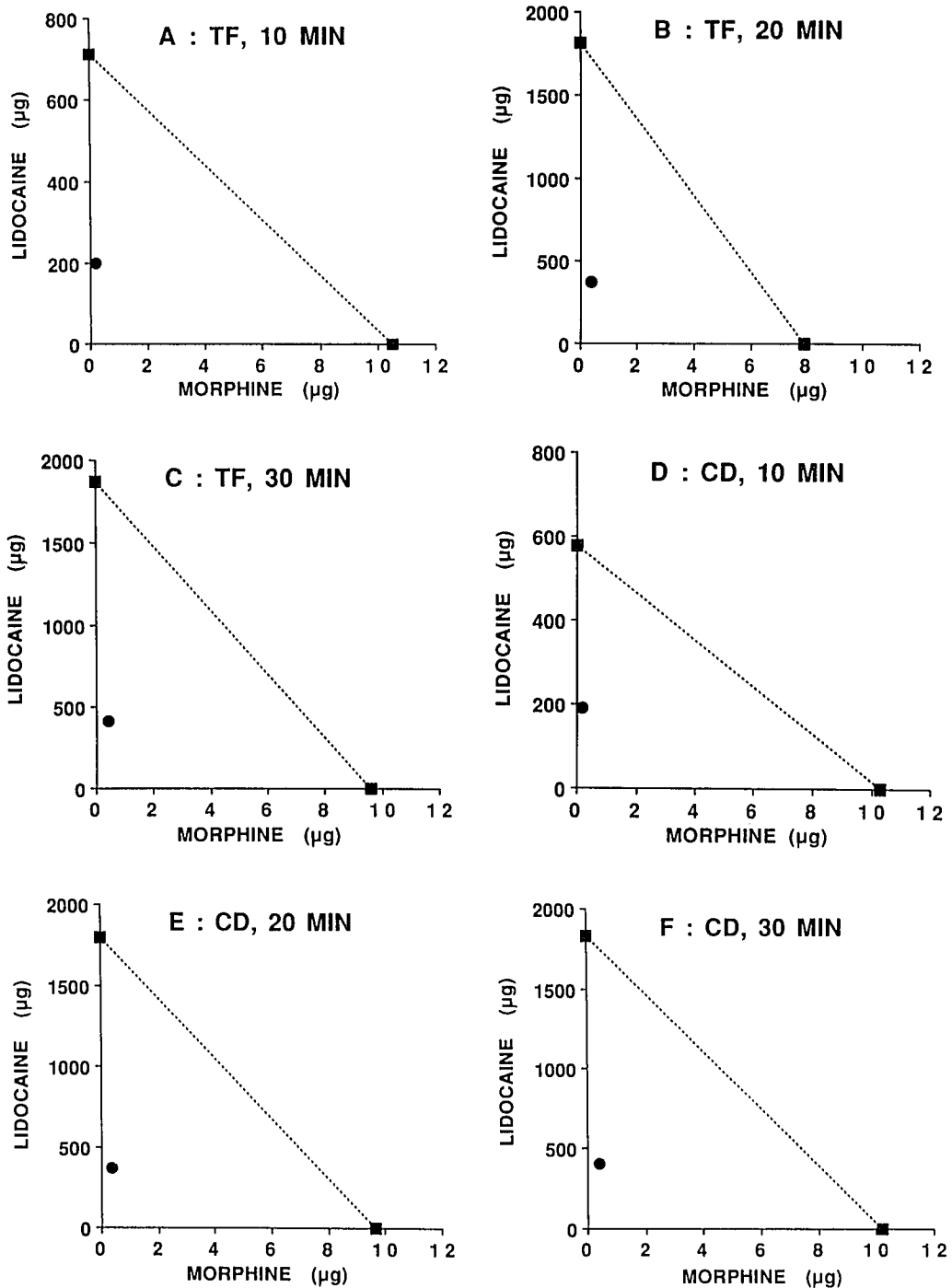


Fig. 8. Isobologram of antinociceptive ED₉₅ (dose producing 95 %MPE) values for morphine (M) alone (squares on the horizontal axis), lidocaine (L) alone (squares on the vertical axis), or the morphine-lidocaine combination (circle in the dose field) in the tail flick (TF) test (A-C) and colorectal distension (CD) test (D-F). The dashed diagonal line represents the theoretical additive line.

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produce synergistic antinociception against both somatic and visceral noxious stimuli. Epidural morphine and lidocaine had dose- and time-dependent antinociceptive effects on both somatic and visceral nociception. With isobolographic analysis, this study quantitatively characterized the synergistic interaction between morphine and lidocaine when administered epidurally. In addition, we confirmed that the duration of antinociceptive effects was prolonged by the combination. This prolongation was demonstrated in (1) time-effect curves for 3 h, (2) isobolograms constructed for the 30-min period after administration, and (3) AUCs for each drug and the combination. Isobolographic analysis revealed the synergistic interaction not only at an earlier time point (10 min) but also at a later time point (30 min). Moreover, AUCs calculated to express overall magnitude and duration of antinociceptive effects were significantly increased by combinations compared with each drug alone, especially with the doses that produced no significant increase in AUC when administered alone.

Recently, spinal opioid-local anesthetic interactions have been reported in several animal studies.¹⁸⁻²⁰ Åkerman *et al.*¹⁸ and Penning and Yaksh,¹⁹ studying mice and rats, respectively, reported synergistic interactions between local anesthetics and opioids using a TF test, a hot-plate test, or a paw-pressure test as measures of somatic pain. Although they demonstrated that intrathecal morphine and lidocaine or bupivacaine increased antinociceptive effects compared to each drug alone, Åkerman *et al.* did not subject their data to standard drug-drug interaction analysis, and neither study addressed the issue of visceral nociception. Using isobolographic analysis, Maves and Gebhart²⁰ showed antinociceptive synergy between intrathecal morphine and lidocaine during visceral and somatic nociception in rats. Although this study clearly showed the synergism between morphine and lidocaine at the time of peak effect for each drug, it did not address prolongation of the duration of the antinociception. Importantly, a recent electrophysiologic study in spinal dorsal horn neurons demonstrated marked potentiation of the inhibition of C-fiber evoked responses of nociceptive neurons by a combination of intrathecal morphine and lignocaine, compared to each agent alone. Moreover, an earlier onset of the inhibition and an increase in duration were observed.²⁹

In those studies,¹⁸⁻²⁰ intrathecal administration was used. Clinically, epidural administration is also commonly used.³⁰ Epidurally administered opioids or local

anesthetics exert their effects by more complicated mechanisms than when administered intrathecally.^{21,22} Epidurally administered drugs potentially enter the neuraxis by three different pathways²¹: (1) directly across the dura into the cerebrospinal fluid; (2) through the perineurium of the mixed spinal nerves into the subperineural space, and then centripetally along the nerve roots to the spinal cord and subarachnoid space; or (3) by rapid uptake into the posterior radicular branch of spinal segmental arteries or into the epidural veins. Differences in pharmacokinetics have been demonstrated between drugs administered epidurally and intrathecally.^{31,32} Therefore, we used an epidural model to clarify whether epidurally coadministered morphine and lidocaine interact synergistically or just additively.

Epidural opioids and local anesthetics have been combined to improve pain relief in postoperative,¹⁻⁷ obstetric,⁸⁻¹¹ and cancer¹²⁻¹⁴ patients. The combination produces greater analgesia than does local anesthetic alone after abdominal,¹⁻³ thoracic,⁴ and gynecologic surgery^{5,6} and during labor.⁸⁻¹¹ In contrast, results from studies comparing epidural combination of local anesthetic and opioid with opioid alone are somewhat conflicting.^{1,4,5,15-17} Many studies demonstrate greater analgesia with the combination than with the opioid alone, but significant differences in both the degree of analgesia and the incidence of side effects were rarely observed. Most clinical studies have used a fixed dose of opioid that was effective by itself in control groups such that it would be difficult to prove synergistic analgesia. Recently, Dahl *et al.*⁷ reported that low doses of epidural morphine and bupivacaine significantly reduced pain compared with morphine alone during mobilization and cough, but not at rest, in patients after major abdominal surgery. Postoperative patients experience more pain during mobilization than at rest. Dahl *et al.* suggest that a combination of opioid and local anesthetic can counteract stronger pain. The current study provides evidence to support excellent analgesia after epidural injection of opioids mixed with local anesthetics, as shown in those previous clinical reports. The clear advantage to using such combinations, as demonstrated in the current study, is the ability to use lower concentrations of each drug, thereby reducing the expected side effects associated with each drug.

Some clinical implications of the present study should be discussed here. First, a problem with clinical studies of analgesic drug interactions is that complete anal-

gesia—*i.e.*, near 100 %MPE, not ED₅₀—is sought. In a study of spinal opioid- α_2 -adrenergic interactions, it was reported that synergism was lost at ED₉₀ (dose producing 90 %MPE), whereas doses producing a lesser effect represented synergism.³³ Therefore, we constructed isobolograms for the doses calculated to produce 95 %MPE from dose-effect curves derived in the current study to examine whether synergistic interaction is maintained at this higher level of drug effect. The experimental dose effective in 95% of subjects for the combination also fell far below the theoretically additive line at every time point evaluated in both TF and CD tests (fig. 8), suggesting that synergistic interaction does exist even at the level of 95% effect, which is a clinically relevant end point. In the current study, a combination of higher doses that alone had significant effects produced lesser interaction than did lower dose combinations. The reason for this is the significant experimental artifact caused by the truncating effect of using a cut-off time or cut-off pressure in the nociceptive test. It is likely that some rats receiving those higher dose combinations and assigned a 100% MPE rating were, in fact, able to tolerate much stronger noxious stimuli than those used in the current study. These explanations can be applied to clinical studies of analgesic drug interaction. The important fact relevant to clinical practice from our study is that lower doses that alone produce just a minimal effect could, in combination, produce almost full effect (near 100% MPE), suggesting that subanalgesic dose combination can produce a high degree of analgesia for the treatment of clinical pain.

Second, lipid-soluble opioids such as fentanyl and sufentanil are most commonly combined with local anesthetics, whereas we studied a poorly lipid-soluble opioid, morphine. Epidurally administered highly lipid-soluble opioids are rapidly absorbed into systemic circulation and exert their effects *via* both spinal and supraspinal mechanisms. Clinical³⁴ and animal³⁵ studies have demonstrated that an important component of the analgesia after epidural administration of fentanyl is provided by its systemic absorption, although a neuroaxial component is not precluded. Because it has been suggested that synergistic interaction between spinal and supraspinal sites accounts for the major portion of the analgesic effect of systemic μ -receptor agonists,³⁶ the magnitude of the analgesic effect after epidural injection of highly lipid-soluble opioids would result from synergistic interaction, and so possibly make it difficult to detect further synergism. Differences in cerebrospinal fluid pharmacoki-

netics between highly lipid-soluble opioids and less soluble opioids may influence the interaction. The fraction of the opioid dose crossing the dura after epidural injection is less in fentanyl than in morphine,³⁷ and epidural meperidine is removed from the cerebrospinal fluid to subarachnoid tissue compartment faster than is morphine.³² Thus, because spinal actions after epidural administration may be small for highly lipid-soluble opioids, the same interaction as that seen with morphine in the current study may not be directly applicable to them.

Visceral pain is of great concern for many clinicians because components of postoperative, obstetric, and cancer-related pain are of visceral origin.³⁸ Recently, Ness and Gebhart developed a model of visceral nociception produced by CD in awake, unrestrained rats.²³ This model is more quantifiable, reproducible, reliable, and closely related to human pathology and less invasive than previous visceral pain models, such as acetoacetic-induced writhing or electrical stimulation. Our study demonstrates that epidural morphine, lidocaine, and their combination have dose- and time-dependent antinociceptive effects on both somatic and visceral nociception. ED₅₀ values and AUCs for morphine, lidocaine, or the combination were similar in the TF test and the CD test.

The isobolographic analysis of dose-response curves of fixed ratios of drugs provides a rigorous means of examining drug-drug interaction.³⁹ We constructed the isobolograms for several time points (10, 20, and 30 min after injection) to determine the nature of the interaction throughout the time-effect course. A synergistic interaction was found at all time points examined, but we may have underestimated the degree of synergism between morphine and lidocaine for two reasons. First, simultaneous administration of morphine and lidocaine would be expected to produce a lesser peak effect than well timed administration, which could make the peak effect of each drug coincide. Well timed administration is commonly used for isobolographic analysis for drugs that have a significant time lag in peak effect.^{20,40} We chose to administer morphine and lidocaine simultaneously because clinically these drugs are administered at the same time by bolus injection or continuous infusion. A second reason is the combined dose ratio. None of the pairs of morphine ED₅₀ and lidocaine ED₅₀ determined in the current study makes a 1:1,000 ratio, indicating that the combined dose ratio of morphine and lidocaine (1:1,000) we used was not equipotent at any time point. The ratio

of drugs used could influence whether the interaction results in synergistic or only additive effect.^{40,41}

The underlying mechanisms of synergism remain to be elucidated. The interactions are clearly complex. An electrophysiologic study has demonstrated that morphine is significantly more potent against spinal visceral than against spinal cutaneous nociceptive transmission,⁴² and a behavioral study has shown that intrathecally coadministered morphine and lidocaine produce greater synergism in visceral nociception than in somatic nociception.²⁰ In the current study, using epidural administration, the effects were similar on visceral and somatic nociception. Opioids and local anesthetics possess different sites and modes of action. The primary mode of action of local anesthetics is sodium channel blockade and axonal conduction blockade. The antinociceptive effect of morphine is considered to take place through interaction with specific opioid receptors.⁴³ In the current study, naloxone completely blocked the enhanced antinociception produced by the combination, demonstrating that in the absence of opioid receptor activity, no synergism can occur. Thus, the synergistic interaction between morphine and lidocaine is mediated, at least partly, by opioid receptors. It has not yet been elucidated whether local anesthetics have a significant interaction with opioid receptors or not. Recently, Tejwani *et al.*,⁴⁴ using radioreceptor assays, found that although combined application of morphine and bupivacaine on rat spinal cord membrane preparations did not produce an increase in the binding of ³[H]-naloxone by morphine to opioid receptors, low concentrations of bupivacaine potentiated the displacement of ³[H]-naloxone by morphine, indicating that in the presence of bupivacaine it is easier for morphine to bind to spinal opioid receptors. They suggested that the facilitation of morphine-induced antinociception by bupivacaine may be associated with a conformational change in the spinal opioid receptors induced by bupivacaine.

The drug combination may effectively inhibit overall neuronal excitability at the level of ionic channels, by blocking sodium channels with lidocaine⁴⁵ and opening potassium channels, hyperpolarizing membranes, and reducing calcium influx with morphine.⁴⁶ Moreover, local anesthetics also have extensive effects⁴⁵ on membrane-associated enzymes and second-messenger systems and on synaptic transmission in the spinal cord, which may be inhibited by local anesthetics through the modification of postsynaptic receptors as well as the blockade of presynaptic calcium channels that must

function to stimulate the release of transmitters. (For a review, see ref. 45.)

Change in the pharmacokinetics of each drug may occur when they are coadministered. It has been reported that intrathecal coadministration of morphine and bupivacaine does not alter the morphine concentration either in spinal cord tissue or in plasma.¹⁹ The plasma fentanyl concentration in patients receiving an epidural fentanyl-bupivacaine mixture was not different from that in patients receiving epidural fentanyl alone.^{16,17} However, the influence of epidural local anesthetics on opioid pharmacokinetics has not yet been systematically evaluated.

In conclusion, our results demonstrate that epidurally coadministered morphine and lidocaine interact synergistically so that both the degree and the duration of analgesia, on both somatic and visceral nociception, are enhanced. This finding may be very important clinically because an appropriate combination of opioid and local anesthetic will be able to provide improved analgesia and at the same time minimize the side effects associated with either drug.

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