

## Antinociceptive Synergy Between Intrathecal Morphine and Lidocaine during Visceral and Somatic Nociception in the Rat

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Clinical investigations have suggested a synergistic interaction between the analgesic effects of intrathecal opioids and local anesthetics; however, basic pharmacologic evidence for this observation has not been reported. Therefore, the authors have used models of visceral and somatic nociception to quantify the interaction between intrathecal morphine and lidocaine in a crossover study of 24 rats in four equal groups. Combinations of morphine and lidocaine were administered separately, corresponding to time of peak effect for each drug. Colorectal distention, as a noxious visceral stimulus, was applied to two groups while cardiovascular and visceromotor responses, respectively, were recorded. A third group received hot plate testing as a somatic nociceptive stimulus. Intrathecal morphine and lidocaine both attenuated the cardiovascular and visceromotor responses to colorectal distention and increased hot plate latencies in a dose- and time-dependent manner. With the use of isobolographic analysis, the coadministration of morphine and lidocaine demonstrated a synergistic, supraadditive interaction during visceral nociception ( $P < 0.001$ ) and somatic nociception ( $P < 0.005$ ). In a fourth group, motor function was evaluated by an inclined screen method. Intrathecal lidocaine in the dosage range tested during isobolographic analysis revealed no motor deficits. These data clearly demonstrate antinociceptive synergy between intrathecal morphine and lidocaine during visceral and somatic nociception at dosages that do not impair motor function. (Key words: Analgesics, opioid: morphine. Anesthetic techniques: intrathecal. Anesthetics, local: lidocaine. Drug interactions: synergy. Pain: somatic; visceral.)

INTRATHECAL/EPIDURAL OPIOIDS and local anesthetics are used frequently to manage visceral and somatic pain. The side effects of intrathecal/epidural opioids are dose-dependent and may be annoying (pruritus, nausea, sedation, and urinary retention) or disastrous (early or late respiratory depression). Intrathecal/epidural local anesthetics may cause hypotension secondary to sympathetic blockade and may limit the ability to walk secondary to motor blockade.

There is evidence that the concomitant use of epidural opioids and local anesthetics may have synergistic effects that achieve control of postoperative and obstetric pain at lesser doses than those necessary with single-drug ther-

apy.<sup>1-5</sup> With reduced drug doses, side effects are minimized and tolerance may be decreased. Other studies conclude that there is no beneficial effect when combining epidural local anesthetic and opioid.<sup>6,7</sup> In addition, local anesthetic/opioid antagonism may occur, as demonstrated by decreased epidural morphine analgesia after epidural 2-chloroprocaine anesthesia.<sup>8</sup>

Epidural interaction studies are plagued with the following question: Is the interaction occurring at a spinal or systemic (supraspinal) site? Systemic effects from epidural agents occur with significant vascular absorption from the epidural space and the large volume and dose of drug required (10-20 times that necessary for an equivalent intrathecal effect). We administered agents intrathecally to clarify the analysis of morphine-lidocaine interaction at spinal sites. Although some clinical studies suggest analgesic synergy between intrathecal/epidural opioid and local anesthetic, basic pharmacologic evidence for this interaction has not been reported.

Quantifying an antinociceptive synergistic effect presents practical and ethical limitations in human subjects; however, animal models of visceral and somatic nociception have been described. Akerman *et al.*<sup>9</sup> reported a synergistic relationship between local anesthetics and opioids using tail-flick and hot plate (HP) latencies as measures of somatic pain in mice. Although this was an important initial study, these data were not subjected to standard drug-drug interaction analysis (for example, isobolographic analysis), and the study did not address the issue of visceral nociception.

A major component of postoperative, obstetric, and oncologic pain is of visceral origin.<sup>10</sup> Cutting, crushing, pinching, and heat applied to human viscera do not produce pain reliably.<sup>11</sup> However, pain is produced reliably in humans during distention of hollow organs.<sup>12</sup> Recently, Ness and Gebhart<sup>13</sup> developed a model of visceral nociception produced by colorectal distention (CRD) in awake, unrestrained rats. In this model, cardiovascular (CV) and visceromotor (VM) responses provide objective measures of visceral nociception. The CRD model has opened a new arena for the study of visceral pain that may correlate better to human pain experiences in the postoperative, obstetric, and oncologic settings.

In this study, we evaluated and quantified the interaction of intrathecal opioids and local anesthetics during visceral and somatic nociception.

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Received from the Departments of Pharmacology and Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa. Accepted for publication September 3, 1991. Supported by National Institutes of Health grant NS 19912 and an unrestricted pain research grant from Bristol-Myers Squibb Company.

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## Materials and Methods

### SUBJECTS

The experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee of the University of Iowa. A crossover study was performed with 24 unanesthetized male Sprague-Dawley rats (Biolab, St. Paul, MN) weighing 280–420 g. Four groups, 6 rats per group, were studied independently. Two groups received distention of the descending colon and rectum as a noxious visceral stimulus, and a third group received HP testing as a somatic noxious (thermal) stimulus. The two groups that received CRD were separated into CV and VM response groups. A fourth group was studied for motor blockade, with the use of an inclined-screen method.

### SURGICAL PREPARATION

All surgical procedures were performed with the rats under deep sodium pentobarbital anesthesia (40–50 mg/kg, intraperitoneally). With the use of the method described by Yaksh and Rudy,<sup>14</sup> an intrathecal catheter (PE 10) was inserted at the atlantooccipital junction and advanced 9 cm to the lower lumbar enlargement in all rats ( $n = 24$ ). The location of the distal end of the intrathecal catheter was verified at the end of the experiment by injection of fast green dye and postmortem examination of the spinal cord. A femoral arterial catheter was implanted for measurement of arterial blood pressure in the CV response, visceral nociceptive group ( $n = 6$ ). Arterial and intrathecal catheters were exteriorized and secured at the back of the head, and 60,000 IU penicillin G (Dual-Pen®; TechAmerica) was injected intramuscularly. Rats exhibiting motor abnormalities were not included in this study. After surgery, rats were housed individually with free access to food and water and allowed to recover for 1 week before use.

### CARDIOVASCULAR RESPONSE: VISCERAL NOCICEPTIVE GROUP

Colorectal distention was produced by air inflation of a 7–8-cm flexible latex balloon inserted intraanally and connected to a pressure-controlled device described previously.<sup>15</sup> Phasic CRD (20-s duration) was produced when a solenoid gate was opened to a constant pressure air reservoir at 80 mmHg, resulting in an instantaneous increase in the balloon pressure to 80 mmHg. Phasic CRD in awake rats results in a reliable, reproducible increase in mean arterial pressure (MAP).<sup>13</sup> The CV response to CRD was measured as the change in MAP ( $\Delta$ MAP) during a 20-s phasic distention to 80 mmHg.  $\Delta$ MAP was defined as the

mean of MAP during distention minus the baseline MAP. Three distentions were performed in unmedicated rats while heart rate, distention pressure, and MAP were monitored simultaneously to establish a baseline CV response to CRD. Drugs then were administered intrathecally, and the CV responses to CRD were recorded every 4 min for ten trials.

### VISCEROMOTOR RESPONSE: VISCERAL NOCICEPTIVE GROUP

In contrast to phasic CRD, ramped CRD was produced by slowly increasing balloon pressure from 0 to 80 mmHg over 10 s, resulting in contraction of the abdominal musculature and a “hunching” behavior, which has been described previously as the VM response.<sup>13</sup> The VM threshold was the distending pressure that resulted in contraction of the abdomen or hind limbs (“hunching” behavior) during ramped CRD. To avoid tissue damage, balloon pressure was not allowed to exceed 80 mmHg. Four ramped CRDs were performed to establish a VM threshold before drug administration. After intrathecal drug administration, each trial consisted of three consecutive ramped CRDs 30 s apart, and the three VM threshold pressures were averaged. Trials were separated by 4 min. A VM threshold pressure of 80 mmHg was recorded for rats not responding by 80 mmHg.

### HOT PLATE RESPONSE: SOMATIC NOCICEPTIVE GROUP

Somatic nociception was measured by the HP method ( $55 \pm 1^\circ \text{C}$ ), as described by Gebhart and Mitchell.<sup>16</sup> Reaction latency was the interval from when the rat was placed onto the surface of the HP until a nociceptive response was observed (e.g., licking a paw or jumping up the side of the testing cylinder). Before HP testing, a conditioning period (five HP trials per day for 3 consecutive days) was applied so learned-response behavior would not affect reaction latencies. Baseline reaction latencies were recorded before drugs were administered intrathecally. After drug injection, reaction latencies were recorded every 4 min for six trials. Rats not responding within 25 s were removed from the plate to prevent tissue damage, and a reaction time of 25 s was recorded.

### MOTOR BLOCKADE

Because lidocaine has significant effects on motor function and this aspect of its pharmacologic profile could influence its “antinociceptive” action measured in the VM and HP tests, the effects of lidocaine given intrathecally on the ability of rats to remain on an 80-degree inclined screen were tested according to the method described by

Domer.<sup>17</sup> The time that the rat remained on the inclined screen without falling was recorded for various doses of intrathecal lidocaine and lidocaine-morphine combinations. Rats remaining on the screen after 1 min were removed, and 1 min was recorded.

## DRUGS AND DRUG INTERACTIONS

The opioid used in this study was morphine sulfate (0.5–5.0  $\mu$ g intrathecally; Merck, Rahway, NJ), and the local anesthetic was lidocaine hydrochloride (62.5–500  $\mu$ g intrathecally; Research Biochemicals, Inc., Natick, MA). The drug solutions were freshly prepared in 0.9% sterile saline in concentrations that allowed intrathecal injections in 10- $\mu$ l volumes. All intrathecal injections were administered manually over 30 s and followed by a 10- $\mu$ l flush of air to clear the catheter and ensure complete drug delivery. All intrathecal drug doses are presented as micrograms of the salt forms described above. Control trials were conducted with 0.9% sterile saline.

All rats in the three nociceptive test groups received all doses of lidocaine, morphine, lidocaine-morphine combination, and vehicle control. There were at least 2 days between successive experiments with any rat after administration of intrathecal morphine. Dose-response curves were derived for morphine and lidocaine. The dose that yielded a 50% change in nociceptive response (MAP, VM threshold, or HP response latency) was defined as the effective dose 50 ( $ED_{50}$ ).

To perform the isobolographic analysis, morphine and lidocaine were administered in combination as fixed ratios of the  $ED_{50}$  dose for each drug. For each group, four dosage combinations were tested ( $ED_{50}$  morphine +  $ED_{50}$  lidocaine; 1/2  $ED_{50}$  morphine + 1/2  $ED_{50}$  lidocaine; 1/4  $ED_{50}$  morphine + 1/4  $ED_{50}$  lidocaine; and 1/8  $ED_{50}$  morphine + 1/8  $ED_{50}$  lidocaine). As determined from preliminary studies, intrathecal lidocaine was injected 20 min and 16 min after intrathecal morphine during visceral and somatic nociceptive testing, respectively, so that the peak effect of each drug coincided. A dose-response curve for the morphine-lidocaine mixture was derived, and the  $ED_{50}$  of the mixture was calculated.

Alteration in cerebrospinal fluid (CSF) pH by morphine and/or lidocaine may affect the pharmacokinetics of the other drug and thus affect the morphine-lidocaine interaction. Although CSF has some buffering capacity, it is less than that of plasma. To reproduce a possible worst-case scenario, we added morphine (0.05 mg/ml and 0.5 mg/ml), lidocaine (6.25 mg/ml and 50.0 mg/ml), and a morphine (0.25 mg/ml)/lidocaine (25.0 mg/ml) mixture to artificial CSF<sup>18</sup> (pH = 7.41) in a 1:20 volume ratio. Study injection volumes of 10  $\mu$ l and rat CSF volume of 200  $\mu$ l were used to establish the 1:20 ratio. Solution pH

was analyzed by a System 1306 pH/blood gas analyzer (Instrument Laboratory, Lexington, MA).

## STATISTICAL ANALYSES

The dose-response curves were evaluated for linearity and deviation from parallelism by a one-way analysis of variance.  $ED_{50}$ s and 95% confidence intervals (CIs) were calculated by a graded  $ED_{50}$  program. Data for  $\Delta$ MAP are reported as the percentage change from baseline MAP (% $\Delta$ MAP<sub>b</sub>). The response for each VM and HP trial was calculated as the maximal possible effect (%MPE):

$$\%MPE (HP) = 100$$

$$\times \frac{\text{test HP latency} - \text{baseline HP latency}}{\text{cut-off time (25 s)} - \text{baseline HP latency}}$$

$$\%MPE (VM) = 100$$

$$\times \frac{\text{test VM threshold} - \text{baseline VM threshold}}{\text{cut-off pressure (80 mmHg)} - \text{baseline VM threshold}}$$

Isobolographic analysis for drug-drug interaction was conducted according to the procedure of Tallarida *et al.*<sup>19</sup> A demonstration isobologram is illustrated in figure 1. Data from individual and combination dose-response curves are used to generate the isobologram. The theo-

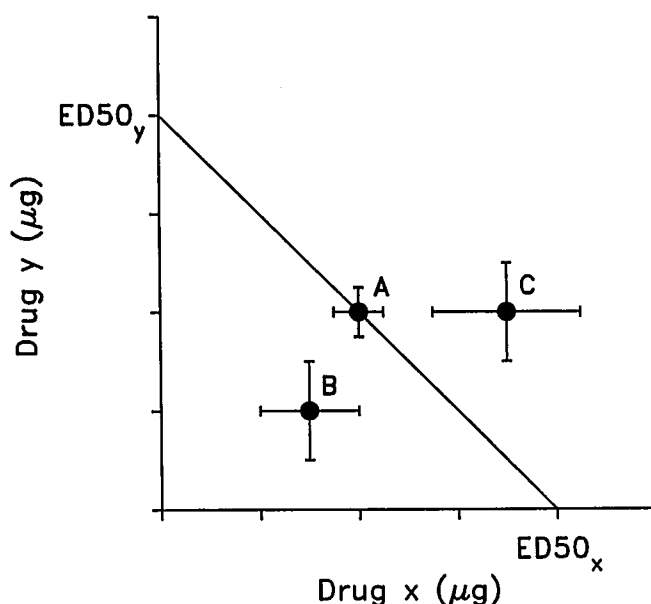


FIG. 1. Demonstration isobologram. The theoretical additive line connects the experimentally determined  $ED_{50}$  dose of drug X with the experimentally determined  $ED_{50}$  dose of drug Y. Any point which falls on this line (A) indicates simple addition of effects of each drug. Any point statistically moved to the left (B) denotes synergy, and a point moved to the right (C) indicates antagonism between drug X and drug Y.

retic additive line is illustrated by the solid diagonal line connecting the  $ED_{50}$  dose of drug X with the  $ED_{50}$  dose of drug Y. If the  $ED_{50}$  dose of the mixture of drugs X and Y falls on the theoretic additive line, the effect of the mixture of drug X and Y is additive (*e.g.*, point A, fig. 1). Points to the left of the theoretic additive line would be consistent with a supraadditive or synergistic interaction (*e.g.*, point B, fig. 1), whereas points to the right of the line would indicate a subadditive or antagonistic interaction (*e.g.*, point C, fig. 1). Confidence intervals for each point were calculated from the variances of each component alone. The CIs were evaluated for statistical significance with a Student's *t* test.

## Results

### VISCERAL NOCICEPTION

The effects of lidocaine and of morphine given intrathecally were dose- and time-dependent (fig. 2). The effects of lidocaine were rapid in onset and relatively short in duration (16–24 min), whereas those of morphine were less rapid in onset and of longer duration (more than 30 min). The effect of lidocaine on the CV and VM responses to CRD was already maximal when first tested 30 s after intrathecal administration (figs. 2A and 2C). At the lesser doses of lidocaine tested (62.5 and 125  $\mu$ g), effects on the CV and VM responses to CRD were short-lived (12 min). At the greatest dose of lidocaine tested (500  $\mu$ g), responses to CRD returned to control levels 20–24 min after intrathecal administration. In contrast to lidocaine, mor-

phine (0.5–5.0  $\mu$ g) produced a peak effect on the CV response to CRD 20 min after intrathecal injection (fig. 2B) and a long-lasting effect on the VM response to CRD (fig. 2D).

Data at the time of peak drug effect are presented in standard dose–response format in figure 3. Intrathecal morphine produced a dose-dependent attenuation of the  $\Delta$ MAP in response to phasic CRD with an  $ED_{50} \pm CI$  of  $2.6 \pm 0.6$   $\mu$ g. Intrathecal lidocaine attenuated the  $\Delta$ MAP in a dose-dependent manner with an  $ED_{50} \pm CI$  of  $290.5 \pm 56.4$   $\mu$ g. The dose–response curve for the coadministration of intrathecal morphine and lidocaine in a fixed ratio of the individual  $ED_{50}$  doses is illustrated in figure 3A. The  $ED_{50} \pm CI$  of the morphine and lidocaine mixture was  $79.8 \pm 29.0$   $\mu$ g for attenuation of CV responses to CRD. Coadministration of half the  $ED_{50}$  doses of morphine and lidocaine (1.3  $\mu$ g morphine + 145.2  $\mu$ g lidocaine = 146.5  $\mu$ g mixture) attenuated the  $\Delta$ MAP to 27% from baseline (see mixture dose–response curve). Simple additive effects would have predicted an attenuation of  $\Delta$ MAP to 50% from baseline.

The VM response threshold to ramped CRD was increased significantly by morphine and lidocaine, with an  $ED_{50} \pm CI$  of  $1.5 \pm 0.2$   $\mu$ g for intrathecal morphine and  $199.6 \pm 51.5$   $\mu$ g for intrathecal lidocaine (fig. 3B). The dose–response curve for the coadministration of a fixed ratio of morphine and lidocaine is illustrated in figure 3B. Coadministration of intrathecal morphine and lidocaine increased the VM threshold response to CRD, with an  $ED_{50} \pm CI$  of  $44.8 \pm 19.9$   $\mu$ g. Coadministration of half the  $ED_{50}$  doses of morphine and lidocaine (1.2  $\mu$ g mor-

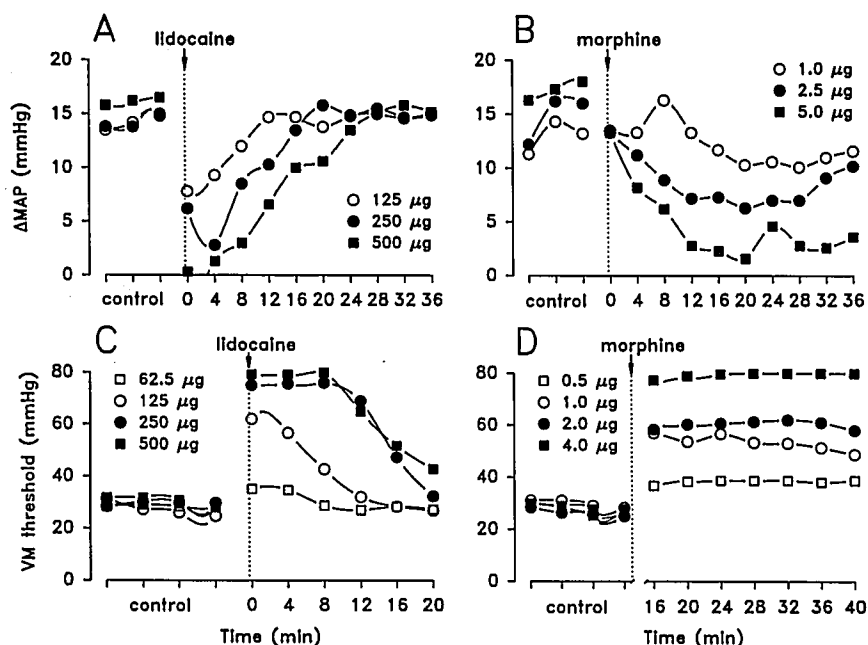
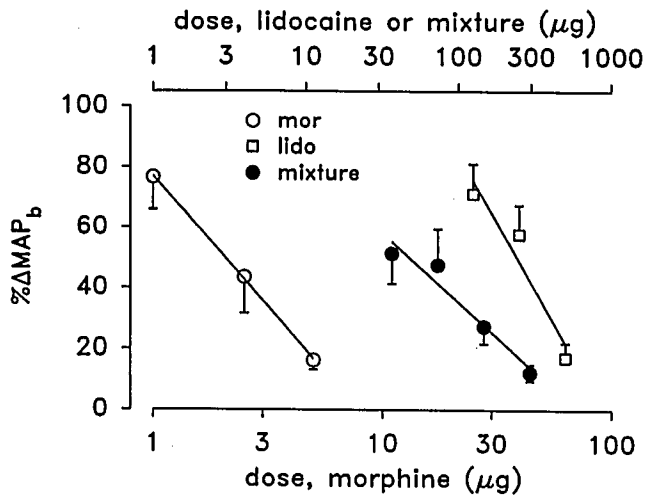


FIG. 2. Time–effect curves for lidocaine and morphine in the visceral nociceptive tests. A, B: Cardiovascular responses, reported as the change from baseline mean arterial pressure ( $\Delta$ MAP) following intrathecal lidocaine (A) or morphine (B) administration. C, D: Visceromotor responses, reported as the visceromotor threshold in millimeters mercury, following intrathecal lidocaine (C) or morphine (D) administration.

### A – Cardiovascular response



### B – Visceromotor response

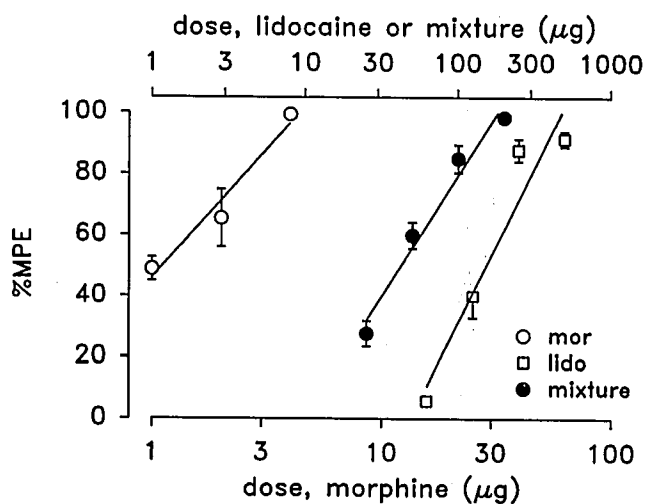


FIG. 3. Dose-response curves for lidocaine, morphine, and a mixture of morphine and lidocaine in the visceral nociceptive tests. A: Cardiovascular responses to colorectal distention, reported as the percent change in mean arterial pressure ( $\% \Delta \text{MAP}_b$ ) from baseline MAP. B: Visceromotor responses to colorectal distention, reported as percent maximal possible effect ( $\% \text{MPE}$ ).

phine + 99.8  $\mu\text{g}$  lidocaine = 101  $\mu\text{g}$  mixture) produced a VM response to CRD at 85% of the maximal possible effect (see mixture dose-response curve). Simple additive effects would have predicted a response at 50% of maximal possible effect.

#### SOMATIC NOCICEPTION

As in the visceral nociceptive tests, the effects of lidocaine and of morphine given intrathecally were both dose- and time-dependent (fig. 4). The effects of lidocaine were

rapid in onset and relatively short in duration (9–13 min), whereas the effects of morphine were less rapid in onset and of longer duration (longer than 30 min). At the lesser doses of lidocaine tested (125 and 250  $\mu\text{g}$ ), effects on HP response latencies lasted 5–9 min. At the greatest dose of lidocaine tested (500  $\mu\text{g}$ ), response latencies returned to control values in 13 min. The peak effect of lidocaine on HP latency was observed when first tested 1 min after intrathecal injection (fig. 4A).

In contrast, morphine produced a peak increase in HP latency 16 min after its intrathecal administration (fig. 4B). At the greatest dose tested (4  $\mu\text{g}$ ), all rats remained at the cutoff latency (25 s) throughout the testing period (28 min). Response latencies at the two lesser doses did not return to control values by 28 min.

When its standard dose-response function was illustrated, intrathecal morphine produced a dose-dependent

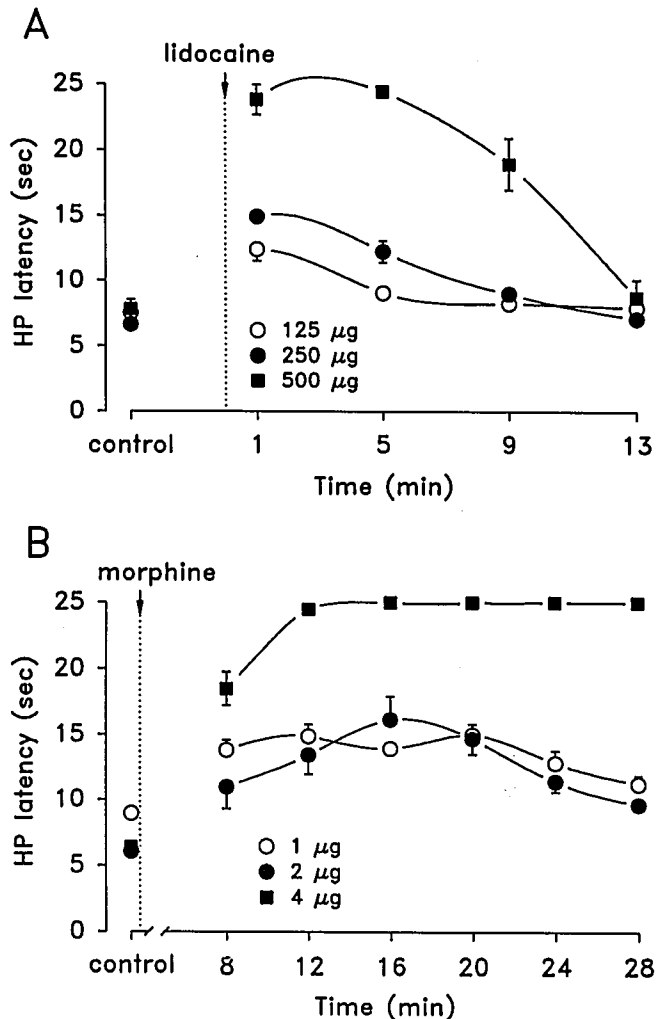


FIG. 4. Time-effect curves for lidocaine (A) and morphine (B) in the hot-plate (HP) test, reported as HP latency in seconds.

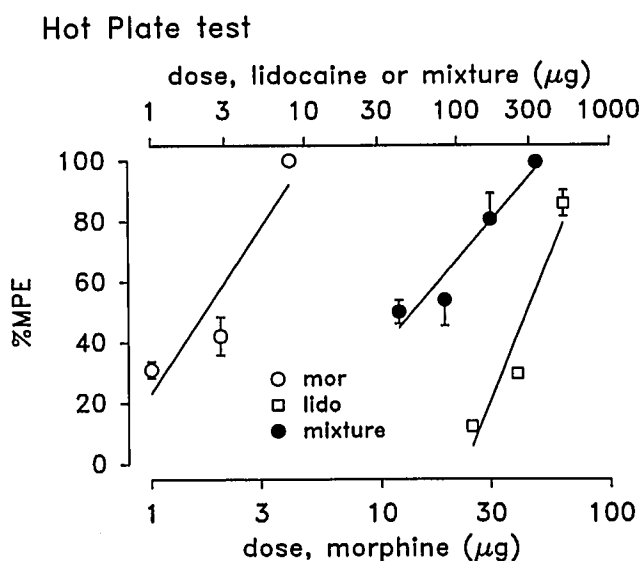


FIG. 5. Dose-response curves for morphine (mor), lidocaine (lido), and a mixture of morphine and lidocaine in the hot-plate test reported as percent maximal possible effect (%MPE).

increase in HP latency with an  $ED_{50} \pm CI$  of  $2.0 \pm 0.2$   $\mu$ g (fig. 5). Intrathecal lidocaine increased HP latency in a dose-dependent manner, with an  $ED_{50} \pm CI$  of  $329.5 \pm 20.1$   $\mu$ g (fig. 5). The dose-response curve for the coadministration of intrathecal morphine and lidocaine is illustrated in figure 5. The coadministration of a fixed ratio of morphine and lidocaine produced an  $ED_{50} \pm CI$  of  $93.9 \pm 38.1$   $\mu$ g during HP testing. Coadministration of half the  $ED_{50}$  doses of morphine and lidocaine ( $1.0$   $\mu$ g morphine +  $165$   $\mu$ g lidocaine =  $166$   $\mu$ g mixture) produced a latency on the HP at 80.5% of the maximal possible effect (see mixture dose-response curve). Simple addition of effects would have predicted a response at 50% of the maximal possible effect.

#### ED<sub>50</sub> SUMMARY

A summary of the  $ED_{50}$  values for morphine, lidocaine, and the mixture is illustrated in figure 6. The morphine  $ED_{50}$  values for CV, VM, and HP responses were not statistically different. The lidocaine  $ED_{50}$  for VM response was statistically different ( $P < 0.05$ ) from the lidocaine  $ED_{50}$  values for CV and HP responses. The mixture  $ED_{50}$ s consisted of 1% morphine and 99% lidocaine as determined by the ratio of the individual  $ED_{50}$  values for morphine and lidocaine (*i.e.*,  $ED_{50}$  morphine<sub>VM</sub> =  $1.5$   $\mu$ g;  $ED_{50}$  lidocaine<sub>VM</sub> =  $199.6$   $\mu$ g). The mixture  $ED_{50}$  values for CV, VM, and HP responses were not statistically different.

#### MOTOR BLOCKADE

Intrathecal lidocaine produced a dose-dependent effect on the ability of rats to remain on a screen inclined to 80

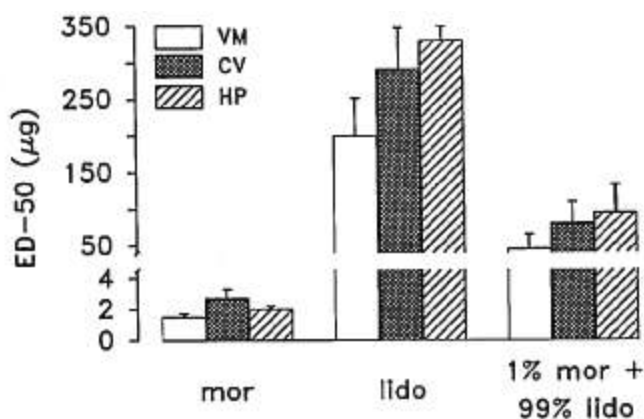


FIG. 6. Summary of  $ED_{50} \pm 95\%$  confidence interval values for morphine (mor), lidocaine (lido), and a mixture of 1% morphine and 99% lidocaine during visceromotor (VM) and cardiovascular (CV) visceral nociceptive tests and hot-plate (HP) somatic nociceptive tests.

degrees (table 1). At the smallest dose of lidocaine tested ( $125$   $\mu$ g), all six rats remained on the screen at 1 and 16 min after intrathecal administration. When tested 1 min after intrathecal administration of lidocaine at a dose of  $250$   $\mu$ g, four rats fell from the inclined screen at 20, 30, 45, and 50 s, respectively. When tested 16 min after intrathecal administration of lidocaine ( $250$   $\mu$ g), all six rats remained on the screen. In contrast, all six rats fell immediately when placed on the inclined screen 1 min after administration of the greatest dose of lidocaine tested ( $500$   $\mu$ g); however, weight bearing was observed to be intact 1 min after this dose of lidocaine. Only two rats fell (at 43 and 50 s) when tested 16 min after intrathecal administration of lidocaine ( $500$   $\mu$ g). These results did not change significantly when  $4$   $\mu$ g intrathecal morphine was administered 20 min before  $125$ ,  $250$ , or  $500$   $\mu$ g intrathecal lidocaine.

#### VEHICLE CONTROL

Intrathecal administration of  $10$   $\mu$ l  $0.9\%$  sterile saline as a single dose or as two consecutive doses 20 min apart produced no significant change in nociceptive response to any test and no evidence of motor deficit (data not shown).

TABLE 1. Motor Blockade

Lidocaine Dose ( $\mu$ g intrathecal)	Time after Lidocaine (min)	Rats Remaining on Screen (number)
125	1	6/6
	16	6/6
250	1	2/6
	16	6/6
500	1	0/6
	16	4/6

# ISOBOLOGRAPHIC ANALYSIS

To assess quantitatively whether drug-drug interactions were greater than additive, as suggested by the data presented above, an isobolographic analysis was necessary. In all three groups (CV, VM, and HP), the dose-response curves for morphine, lidocaine, and the mixture were linear and did not deviate significantly from parallelism. The theoretic additive  $ED_{50} \pm CI$  for the combination of morphine and lidocaine was calculated by the method of Tallarida *et al.*<sup>19</sup>

The experimentally determined mixture  $ED_{50} \pm CI$  for the CV response to CRD was  $0.8 \pm 0.3 \mu g$  for morphine and  $79.0 \pm 29.7 \mu g$  for lidocaine. This point is plotted as 0.8, 79.0 on the CV response isobologram (fig. 7A). The theoretic additive  $ED_{50} \pm CI$  was calculated to be  $1.4 \pm 0.1 \mu g$  for morphine and  $138.4 \pm 6.6 \mu g$  for lidocaine. The CIs of these points do not overlap, and results of a Student's *t* test for potency ratio were significant ( $P < 0.001$ ). Thus, the interaction of lidocaine and morphine in the CV response to CRD is supraadditive or synergistic. As illustrated in figures 7B and 7C, the interactions of lidocaine with morphine in the VM and HP tests, respectively, are also clearly synergistic.

The isobolographic calculations for the VM response to CRD produce a theoretic additive  $ED_{50} \pm CI$  of  $0.84 \pm 0.04 \mu g$  for morphine and  $83.52 \pm 4.64 \mu g$  for lidocaine (fig. 7B). The experimentally determined  $ED_{50} \pm CI$  was  $0.45 \pm 0.2 \mu g$  for morphine and  $44.35 \pm 22.8 \mu g$  for lidocaine. The two points were compared by a Student's *t* test for relative potency and found to be significantly different ( $P < 0.001$ ).

The experimentally determined  $ED_{50} \pm CI$  for the response to HP testing was  $0.9 \pm 0.5 \mu g$  for morphine and  $93.0 \pm 45.5 \mu g$  for lidocaine. The theoretic additive  $ED_{50} \pm CI$  was calculated to be  $1.25 \pm 0.05 \mu g$  for morphine and  $123.75 \pm 5.10 \mu g$  for lidocaine (fig. 7C). The CIs of these points do not overlap, and the potency ratio was significantly different ( $P < 0.005$ ).

## CSF pH ALTERATION

In vitro addition of 0.5 ml morphine (0.05 mg/ml and 0.5 mg/ml) to 10 ml artificial CSF<sup>18</sup> ( $pH = 7.41$ ) did not alter the solution  $pH$  (7.47 and 7.45, respectively). However, addition of 0.5 ml lidocaine (6.25 mg/ml and 50.0 mg/ml) to 10 ml artificial CSF decreased the solution  $pH$  (7.25 and 6.85, respectively). Combining 0.25 ml morphine 0.25 mg/ml and 0.25 ml lidocaine 25.0 mg/ml with 10 ml artificial CSF decreased the  $pH$  to 6.92.

## Discussion

This study clearly has shown the following: 1) intrathecal morphine and lidocaine have dose- and time-depen-

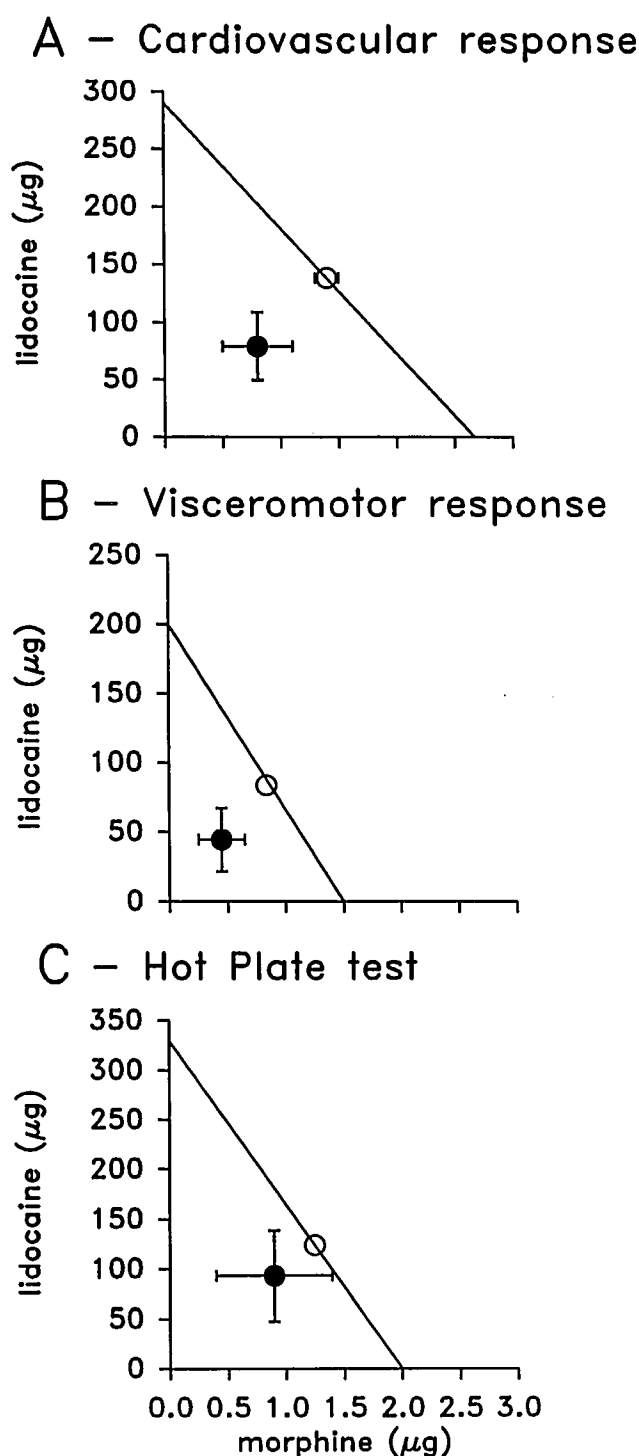


FIG. 7. Isobolograms for intrathecal coadministration of lidocaine with morphine in the visceral nociceptive (cardiovascular [A] and visceromotor [B]) and somatic (hot-plate [C]) nociceptive tests. The solid diagonal line represents the additive line constructed by joining the  $ED_{50}$  dose of lidocaine with that of morphine in the three different tests. The 95% confidence intervals for the lidocaine (vertical) and morphine (horizontal) components of the  $ED_{50}$  are indicated for the actual mixture (solid circle) and for the theoretical additive point (open circle).

dent antinociceptive effects; and (2) at dosages that do not affect motor function, opioids and local anesthetics produce greater antinociception than predicted by simple addition of effects on both visceral and somatic nociception. When the mixture  $ED_{50}$  was compared with the theoretic additive  $ED_{50}$ , visceral nociceptive responses displayed statistically greater synergism than did the somatic nociceptive responses. This may indicate that visceral nociception is more sensitive than somatic nociception to the synergistic interaction of morphine and lidocaine, but such an interpretation requires additional investigation. For example, we cannot assume that the intensities of the distending visceral and thermal somatic stimuli are equivalent. Nevertheless, the current results suggest that visceral pain may be particularly amenable to such combination treatment. This interpretation is supported by earlier work that established that morphine was significantly more potent against spinal visceral than spinal cutaneous nociceptive transmission.<sup>20</sup>

The current study quantitatively characterized the antinociceptive, synergistic interaction between morphine and lidocaine. The clinical implications of this study are clearly important in defending the use of intrathecal drug combinations for improved pain management. Intrathecal/epidural opioids and local anesthetics have been combined to improve the management of visceral pain in postoperative, obstetric, and oncologic patients.<sup>1-5</sup> For example, in a randomized, prospective study, Logas *et al.*<sup>5</sup> found that patients who received continuous thoracic epidural analgesia with morphine and bupivacaine after thoracotomy had lower McGill Pain Questionnaire scores and requested less supplemental opioids than patients who received continuous thoracic epidural analgesia with morphine or bupivacaine alone. Chestnut *et al.*<sup>1</sup> reported that, during vaginal delivery in nulliparous women, a continuous epidural infusion of 0.0625% bupivacaine/0.0002% fentanyl produced equal analgesia, with significantly less motor blockade, to that provided by the infusion of 0.125% bupivacaine alone. Cunningham *et al.*<sup>21</sup> demonstrated improved analgesia with intrathecal amethocaine (Pontocaine®; Winthrop Pharmaceuticals, New York, NY) and morphine for transurethral prostatectomy.

Neither Badner *et al.*,<sup>7</sup> studying low-dose bupivacaine interaction with epidural fentanyl analgesia in postoperative orthopedic patients, nor Douglas *et al.*,<sup>6</sup> evaluating bupivacaine as an adjuvant to epidural morphine after cesarean section, were able to demonstrate a beneficial effect by combining local anesthetic and opioid. However, most clinical studies compare a fixed dose of opioid with and without local anesthetic. The fixed opioid dose is often therapeutic itself, thus limiting the ability to observe a synergistic interaction. To evaluate analgesic interaction and side-effect alteration, future clinical studies should compare subanalgesic dose combinations of local anesthetic and opioid with analgesic doses of each agent alone.

Synergistic interactions can occur when drugs affect different critical points along a common pathway.<sup>22</sup> Intrathecal local anesthetics block action potential generation and propagation. Butterworth and Strichartz<sup>23</sup> recently reviewed the molecular mechanisms of local anesthetic action, and it is clear that local anesthetics block nerve transmission by interacting with individual sodium channels and converting the channel from an open, resting, or closed state to an inactivated form. Although sodium channel blockade is considered to be the primary mode of action, local anesthetics also have extensive effects on membrane-associated enzymes and second-messenger systems such as adenylate cyclase.<sup>24,†</sup> Presynaptic calcium channels also are inhibited by local anesthetics,<sup>25</sup> thereby reducing the amount of neurotransmitter released during depolarization.<sup>26</sup> Thus, local anesthetics have effects on synaptic transmission in addition to their effects on nerve conduction. In contrast, intrathecal opioids exert their effects through receptor-specific interactions in the dorsal roots and dorsal horn of the spinal cord.<sup>27</sup> Opioids may reduce neuronal transmission through inhibition of post-synaptic cell firing or through presynaptic reduction of neurotransmitter release.<sup>28</sup> In addition, opioids can increase a potassium conductance in presynaptic neuronal membranes, resulting in membrane hyperpolarization and a decrease in excitability.<sup>29</sup>

There is no convincing evidence that local anesthetics have a significant interaction at opioid receptors, but Kosterlitz and Wallis<sup>30</sup> reported that opioids may have a nonspecific interaction with excitable membranes, producing a local anesthetic effect. Maruyama *et al.*<sup>31</sup> found that anesthetic doses of morphine (1 mg/kg) decreased responses from a primary afferent volley, suggesting a direct effect on spinal afferents. In contrast, opioids do not affect transmission through rat sensory ganglion.<sup>32</sup>

Addition of local anesthetic may alter opioid pharmacokinetics (*i.e.*, change tissue pH or drug clearance) and thus contribute to the synergistic interaction. *In vitro* addition of lidocaine, but not morphine, to artificial CSF caused a significant decrease in solution pH. It must be determined whether this decrease in pH occurs *in vivo* and what significance it may have on local anesthetic/opioid analgesic synergy. Additional research is required to characterize pharmacokinetic and pharmacodynamic alterations when intrathecal/epidural opioid and local anesthetic are coadministered. Although the mechanisms of synergism between local anesthetics and opioids remain unknown, it is likely that effects on sodium, potassium and calcium channels, intracellular enzyme systems, and altered pharmacokinetics play contributory roles.

† Gordon LM, Dipple ID, Sauerheber RD, Esgate JA, Houslay MD: The selective effects of charged local anesthetics on the glucagon and fluoride-stimulated adenylate cyclase activity of rat-liver plasma membranes. *Journal of Supramolecular Structure* 14:21-32, 1980.

In summary, this study quantified antinociceptive synergy between intrathecal morphine and lidocaine. A synergistic interaction was clearly demonstrated at dosages that did not impair motor function. Both visceral and somatic models were studied, and visceral nociception appeared to be more sensitive than somatic nociception to the synergistic interaction. The results of clinical studies involving opioid and local anesthetic combinations suggest enhanced pain relief and fewer adverse effects. Although caution should be exercised when extrapolating nonhuman animal data to the clinical experience, the results obtained provide convincing justification for the coadministration of intrathecal opioids and local anesthetics to improve pain management while decreasing tolerance and adverse drug effects.

The authors thank Timothy J. Ness, M.D., Ph.D., for assistance in designing this experiment, Michael Burcham for preparing the graphics, and Marilyn Kirkpatrick for assistance in preparing this manuscript.

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