

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

### Effects on the Development of Tolerance to Morphine

Yoji Saito, M.D.,\* Megumi Kaneko, M.D.,† Yumiko Kirihara, D.V.M.,‡ Shinichi Sakura, M.D.,§ Yoshihiro Kosaka, M.D.||

**Background:** There has been little information regarding the effects of local anesthetics on tolerance to opioids, although chronic use of combination of opioids and local anesthetics is popular for pain control. This study was designed to examine the effects of lidocaine on morphine tolerance to somatic and visceral antinociception.

**Methods:** Rats received a continuous intrathecal infusion of morphine ( $0.3\text{--}10\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ), lidocaine ( $30\text{--}1000\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ), a combination of those, or saline. After 6-day infusion, intrathecal morphine challenge test ( $5\text{ }\mu\text{g}/10\text{ }\mu\text{l}$ ) was performed, and time-response curve was constructed to assess the magnitude of tolerance. The tail flick (TF) test and colorectal distension (CD) test were used to measure somatic and visceral antinociceptive effects, respectively.

**Results:** Antinociceptive effects in the TF and CD tests caused by morphine challenge were reduced ( $P < 0.01$ ) in the morphine infused groups. The magnitude of the tolerance was inversely associated with the amount of morphine infused. Lidocaine infusion induced no different change in the morphine challenge test from that seen in the saline infusion group. Development of tolerance was greater in morphine  $3\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  than in morphine  $0.75\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  + lidocaine  $150\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  despite their similar antinociceptive effects during intrathecal infusion. The infusion of a low dose of morphine ( $0.3\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) did not reduce the antinociceptive effects in the challenge test.

**Conclusion:** Lidocaine in combination with morphine does not reduce tolerance to morphine nor develop cross-tolerance. The intrathecal infusion of morphine induced tolerance to so-

matic and visceral antinociception in a dose-dependent fashion. (Key words: Analgesia; attenuation; continuous; spinal.)

PATIENTS suffering from chronic pain often require long-lasting use of opioids or local anesthetics *via* intrathecal or epidural routes. The chronic use of opioids is associated with tolerance, leading to decreased analgesic effects, and associated increased dosing and side effects.<sup>1</sup> Reports have demonstrated the development of opioid tolerance to antinociceptive effects in the spinal cord.<sup>2-5</sup> There are several ways by which local anesthetics could influence opioid tolerance. The development of opioid tolerance was associated with changes in neuronal intracellular calcium levels.<sup>6-8</sup> Local anesthetics depress the voltage-gated calcium current and intracellular calcium ion level in neurons.<sup>9,10</sup> Those observations suggest that local anesthetics might modulate the development of opioid tolerance through those actions sites around the spinal cord. However, the effect of local anesthetics on the development of tolerance to opioids has not been studied.

We have demonstrated, in the companion paper, that synergy between morphine and lidocaine exists during a 6-day intrathecal infusion. Therefore, we can assume that a decrease of required opioid caused by a synergistic analgesic action when opioids are used in combination with local anesthetic may lead to decreased development of tolerance because the development of tolerance depends on receptor occupancy.<sup>11</sup>

The aim of this study was to determine if the presence of lidocaine in a continuous intrathecal infusion with morphine altered the development of tolerance to somatic and visceral antinociception of morphine in rats.

### Materials and Methods

This study was approved by the Animal Research and Use Committee of Shimane Medical University. Full de-

\* Associate Professor.

† Instructor.

‡ Research Associate.

§ Assistant Professor.

|| Professor and Chairman.

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Address reprint requests to Dr. Saito: 89-1 Enya-cho, Izumo, Shimane 693, Japan. Address electronic mail to: ysaito@shimane-med.ac.jp

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tails of the methods, including initial preparation and nociceptive tests, are presented in the companion paper. Methods are briefly described here.

Male Sprague-Dawley rats were divided into 14 equal groups ( $n = 7$ ). One of the following regimens was intrathecally infused for 6 days. The mean body weight of animals before the morphine challenge was noted in parentheses.

1. Morphine hydrochloride;  $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $318 \pm 14$  [ $\pm$  SD] g),  $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $312 \pm 16$  g),  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $303 \pm 8$  g),  $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $308 \pm 15$  g),  $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $318 \pm 19$  g).
2. Lidocaine hydrochloride;  $30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $307 \pm 16$  g),  $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $304 \pm 8$  g),  $600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $308 \pm 12$  g),  $1000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $318 \pm 16$  g).
3. Combination (morphine hydrochloride + lidocaine hydrochloride);  $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} + 200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $319 \pm 17$  g),  $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} + 600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $315 \pm 12$  g),  $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} + 150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $319 \pm 12$  g),  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} + 30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $317 \pm 16$  g).
4. Normal saline ( $311 \pm 18$  g).

After 6 days of continuous intrathecal infusion, a time-response curve after an intrathecal morphine challenge test was constructed to assess the magnitude of tolerance. On the evening of day 6, the PE-20 part of the intrathecal catheter was cut, and  $10 \mu\text{l}$  of normal saline was injected to clear the residual volume of morphine in the catheter. Fifteen hours later, the tail flick (TF) and colorectal distension (CD) tests were performed before and 10, 20, 30, 60, 90, 120, and 180 min after the bolus intrathecal injection of morphine ( $5 \mu\text{g}/10 \mu\text{l}$ ).

Tail flick latency and CD threshold were converted to percentage maximum possible effect (%MPE) as defined in the companion paper. To evaluate the magnitude of morphine tolerance, area under the curve (AUC) was calculated from the time-response curve (%MPE) of the morphine challenge test using the trapezoidal integration method. All data are presented as mean  $\pm$  SD. Changes in %MPE after intrathecal injection were analyzed using two-way analysis of variance (ANOVA) for repeated measures followed by Scheffe's *post hoc* test. Differences in AUC between groups were analyzed by one-way ANOVA and Scheffe's test for *post hoc* comparison. A  $P$  value  $< 0.05$  was considered to be statistically significant.

## Results

Ten of 98 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 86 rats.

The baseline values (determined 15 h after catheter flush and just before morphine challenge) in the TF and CD tests were not significantly different among all groups, except for the group that received lidocaine  $1000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . After lidocaine infusion at  $1000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , the animals showed increased mean baseline values of  $4.6 \pm 0.4$  ( $\pm$  SD) s and  $24.7 \pm 3.9$  mmHg in the TF and CD tests, respectively, and those values were used for calculating %MPE. Slight motor impairment was shown in three of six rats after a 6-day infusion of lidocaine at  $1000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . However, no rats showed apparent motor impairment 15 h after the end of intrathecal infusion.

### Challenge Test after Morphine Infusion

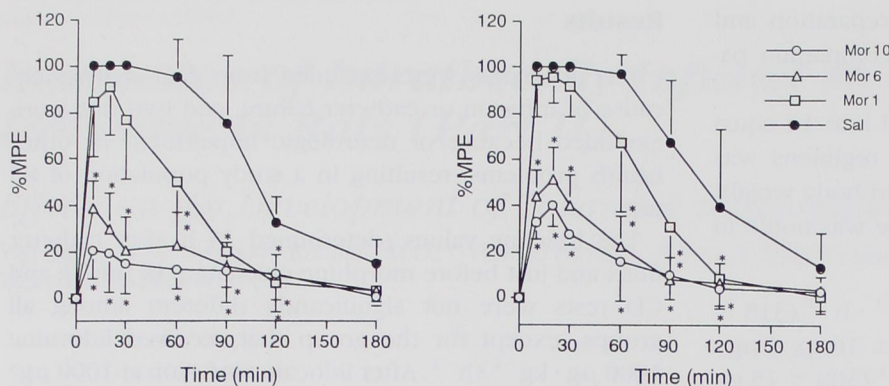
The increases of %MPEs as well as their duration in the TF and CD tests caused by morphine challenge were significantly smaller ( $P < 0.05$ ) in the morphine infusion groups when compared with those in the saline infusion group (fig. 1). The magnitude of the inhibition was inversely associated with the amount of morphine, and that tendency was similar between TF and CD tests.

### Challenge Test after Lidocaine Infusion

In contrast, as shown in figure 2, 6 days of lidocaine infusion caused no change in the morphine challenge effects from that seen in animals that received a saline infusion for 6 days. The peak (100 %MPE), duration of peak effect, and return to baseline values were all similar, even though, as shown in the companion paper, lidocaine infusion produced dose-dependent antinociception and tachyphylaxis.

### Challenge Test after Morphine and Lidocaine Coinfusion

During the 6-day infusion studies, these three doses close to their  $\text{ED}_{50}$ s—morphine  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , lidocaine  $600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ , or morphine  $0.75 +$  lidocaine  $150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ —produced antinociceptive effect that was similar as seen in the AUC plots (inserts) in figure 3. This therefore provided a consistent baseline for examination of the effects of a challenge dose of morphine. Despite their similar antinociceptive effects



ences ( $P < 0.01$ ) between Mor 1 and Sal groups from 60 min to 120 min but not from 10 min to 30 min. In Mor 10 infusion group, %MPE in the TF test was almost completely inhibited to less than 20 %MPE, but %MPE in the CD test demonstrated 40% at peak. Data are presented as mean  $\pm$  SD. \*Significantly different from Sal.

during infusion, figure 3 indicates that tolerance to somatic and visceral antinociception developed in the order of morphine, morphine + lidocaine, and lidocaine.

Figure 4 demonstrates that the time-effect curves in both TF and CD tests for the coinfusion of morphine  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  + lidocaine  $30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  were almost comparable to those for the same dose of morphine ( $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) alone, indicating similar degrees of tolerance development. In contrast, the coinfused group showed greater antinociceptive effect ( $P < 0.05$ ) than the morphine-infused group indicated by the AUC inserted in the figure 4.

When the low dose of morphine ( $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) is used for intrathecal infusion, the infusion of morphine alone as well as the coinfusion of the same dose morphine with lidocaine  $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  or lidocaine  $600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  showed no significant differences from saline infusion group in %MPEs in TF and CD tests in morphine challenge test (fig. 5). However, antinociceptive effects assessed by AUCs in TF and CD tests for 6-day

infusion were significantly increased ( $P < 0.05$ ) by the combination of lidocaine and that potentiation depended on the dose of lidocaine (fig. 5, insert).

## Discussion

The significance of this study is that coinfused lidocaine could not directly attenuate the development of tolerance to morphine as shown in the challenge test after coinfusion of morphine and lidocaine in figure 4. The lack of lidocaine effect on tolerance development was evident in the presence of both somatic and visceral noxious stimuli. It appears that lidocaine does not modulate the intracellular changes in the development of tolerance to morphine. The mechanisms responsible for the potentiated antinociceptive interaction between lidocaine and morphine appears to be different from those responsible for the development of tolerance.

Most agents, including other opioid agonists,  $\alpha_2$  ago-

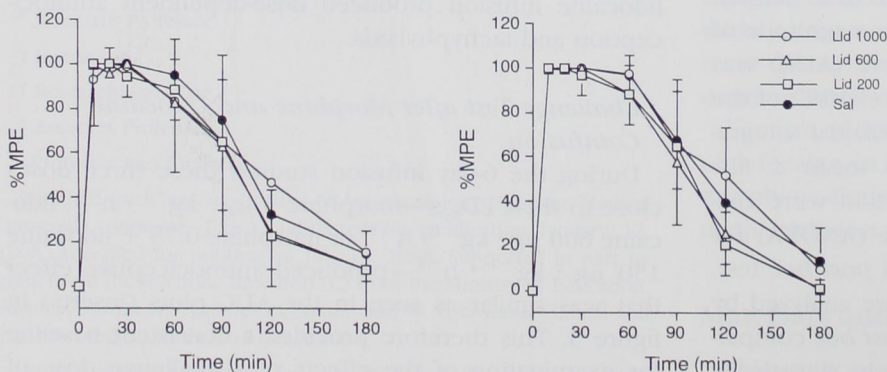
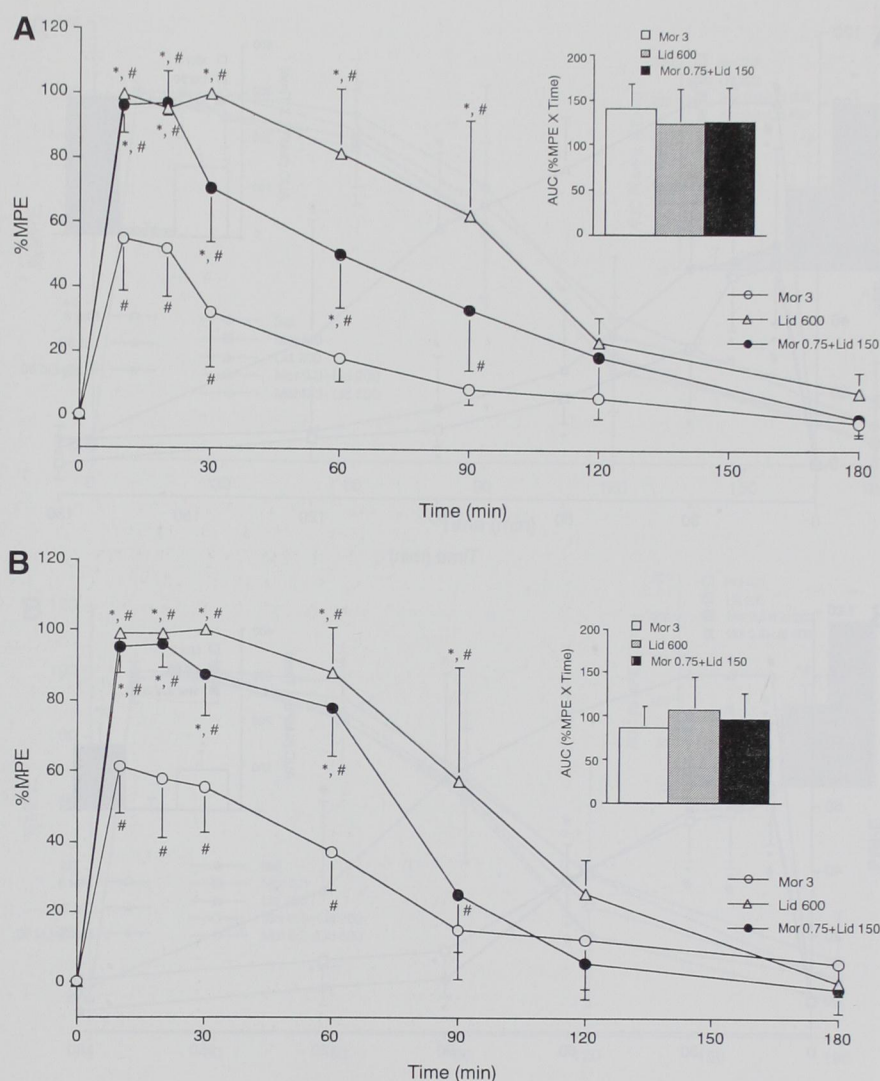


Fig. 2. Time course of effects on %MPE in tail flick test (left panel) and colorectal distension test (right panel) after intrathecal challenge test with morphine (Mor)  $5 \mu\text{g}$  in rats that received intrathecal infusion of lidocaine (Lid)  $200 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), Lid  $600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), Lid  $1000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), or saline (Sal) ( $n = 7$ ) for 6 days. Lid infusion groups caused no change in the time course effects, the peak (100 %MPE), and duration of peak effect, comparing with Sal infusion group. Time course change in %MPEs in both the TF and CD tests after morphine challenge showed a similar tendency in Lid infusion groups. Data are presented as mean  $\pm$  SD. \*Significantly different from Sal.

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Fig. 3. Comparison in time course of effects on %MPE in tail flick test (panel A) and colorectal distension test (panel B) after intrathecal challenge test with morphine (Mor)  $5 \mu\text{g}$  after the intrathecal infusion of Mor  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), lidocaine (Lid)  $600 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ) or Mor  $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  + Lid  $150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), which produced similar antinociceptive effects as shown by AUC for 6 days (inside panels). AUC plots (inserts) show that Mor 3, Lid 600, or Mor 0.75 + Lid 150 produced similar antinociceptive effects during the 6-day infusion. In the morphine challenge tests, %MPEs in both the TF and CD tests in Lid 600 group were significantly higher ( $P < 0.01$ ) than those in Mor 3 group from 10 to 90 min and those in Mor 0.75 + Lid 150 group were also higher ( $P < 0.01$ ) than those in Mor 3 group from 10 to 60 min. Data are presented as mean  $\pm$  SD. #Significantly different from baseline value. \*Significantly different from Mor 3.



nists, and cholecystokinin antagonists, which enhance opioid analgesia,<sup>12,13</sup> cause the cross-tolerance to morphine analgesia.<sup>14,15</sup> Lidocaine, however, did not cause cross-tolerance with morphine in this study, whereas lidocaine enhanced morphine antinociception. This is an important finding, demonstrating a clinical relevance of intrathecal or epidural coinfusion of local anesthetic with opioid. Even if lidocaine does not have a direct inhibition of development of morphine tolerance, the lack of cross-tolerance means that the drugs may be used together effectively and that lidocaine can produce analgesia in patients who have become tolerant.

There was no significant suppression of the antinociceptive effect in the morphine challenge test with or without coinfusion of lidocaine when a low dose of morphine ( $0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) was infused, indicating

no apparent spinal development of tolerance to that low-dose morphine. Of particular importance is that even such a low dose of morphine, which, by itself, produced neither antinociception nor tolerance, can produce synergistic antinociceptive effects when a sub-effective dose of lidocaine is coinfused with it. With higher doses of morphine that produce tolerance, coinfusion of morphine and lidocaine also produced potentiated antinociception but developed tolerance similar to that after the morphine infusion alone. When comparing the doses of morphine required for producing the same antinociceptive effect, the morphine dose was smaller in the lidocaine coinfused group than that in the morphine group, so the magnitude of tolerance to morphine was lower in the coinfused group. The observation may imply that, even if the development of tolerance to mor-

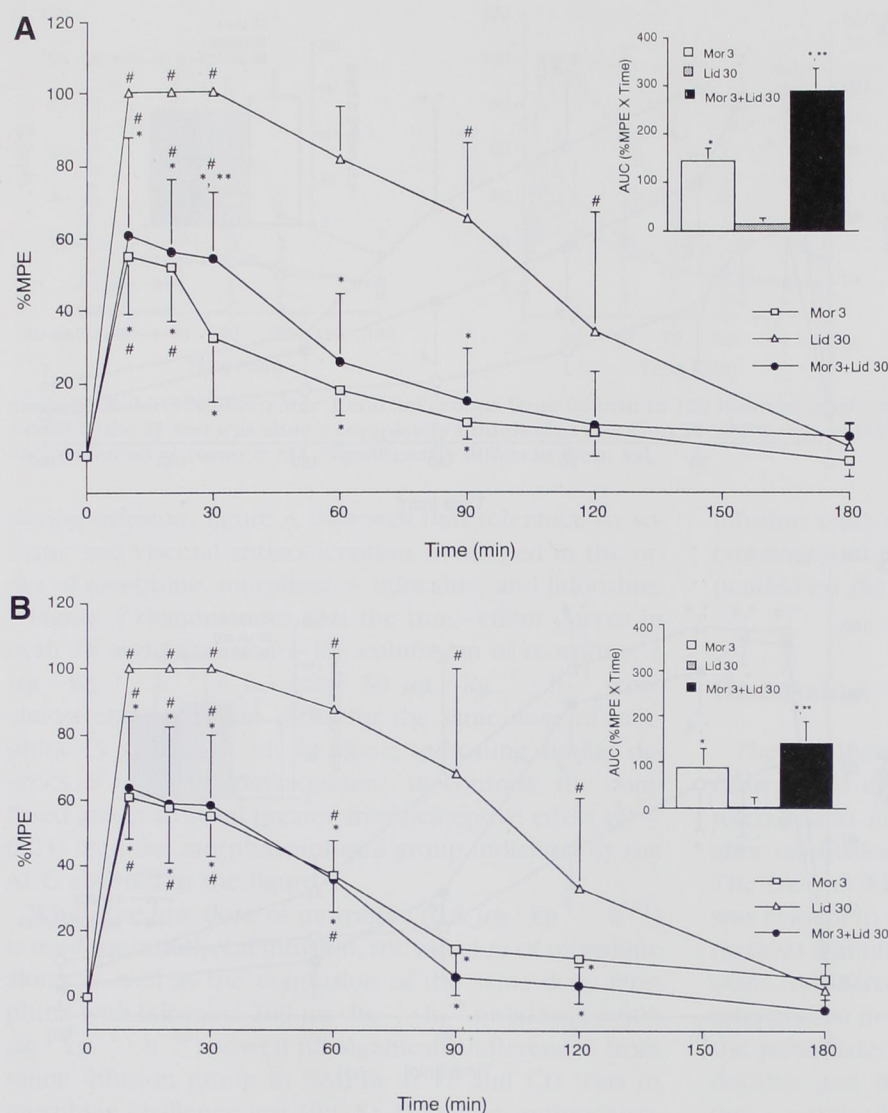


Fig. 4. Comparison in time course effects on %MPE in tail flick test (panel A) and colorectal distension test (panel B) after intrathecal challenge test with morphine (Mor)  $5 \mu\text{g}$  in rats that received intrathecal infusion of Mor  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), lidocaine (Lid)  $30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ), or Mor  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  + Lid  $30 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  ( $n = 6$ ). Inside panels represent area under the curve (AUC) calculated from time-effect curve in intrathecal infusion for 6 days. The time effect curves in TF and CD tests for Mor 3 + Lid 30 were similar to those for Mor 3, with regard to the onset and magnitude of peak effect and the duration of action despite the greater AUC in Mor 3 + Lid 30 infusion ( $P < 0.05$ ) than Mor 3 infusion (inserts). Data are presented as mean  $\pm$  SD. #Significantly different from baseline value. \*Significantly different from Lid 30. \*\*Significantly different from Mor 3.

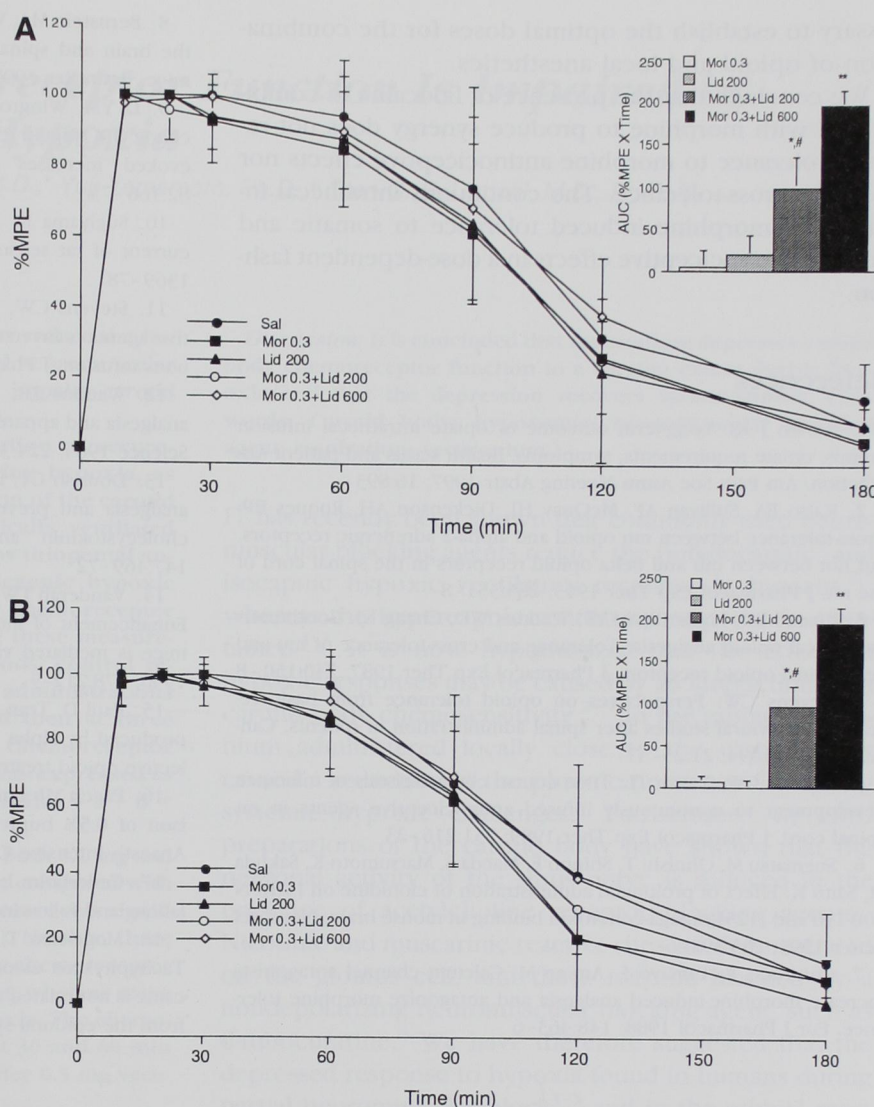
phine is not directly altered by coadministered lidocaine, the ability of lidocaine to reduce the amount of morphine required may, by itself, reduce the likelihood of tolerance developing to morphine because the potentiated antinociception of morphine by lidocaine may contribute to the lower fractional occupancy of the total opioid receptor, which would be expected to cause the less-graded development of tolerance.<sup>11</sup>

Those observations indicate an important direction for the combination opioids with local anesthetics to control the development of tolerance to opioids and produce satisfactory analgesia. The antinociceptive effect of morphine is potentiated by lidocaine depending on the dose of lidocaine as shown in the insert of figure 5 and in the companion paper. Therefore, we should chose

the lowest dose of opioid at the beginning of the epidural or intrathecal coinfusion and keep the dose of opioid as small as possible by changing the dose of local anesthetic to produce satisfactory analgesia because the development of tolerance depends on the dose of morphine and because a low dose of morphine may not develop apparent tolerance. One problem in increasing dose of local anesthetics is appearance of motor block, depending on the dose of local anesthetics. Considering motor block, bupivacaine and ropivacaine may prove even more effective for these combinations because these local anesthetics have stronger analgesic effects and less motor block than lidocaine.<sup>16,17</sup>

Morphine tolerance was seen for both visceral and somatic stimuli with and without lidocaine coinfusion.

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**Fig. 5.** Comparison in time course effects on %MPE in tail flick test (panel A) and colorectal distension test (panel B) after intrathecal challenge test with morphine (Mor) 5 µg in rats that received intrathecal infusion of Mor 0.3 µg · kg<sup>-1</sup> · h<sup>-1</sup> (n = 6), lidocaine (Lid) 200 µg · kg<sup>-1</sup> · h<sup>-1</sup> (n = 6), Mor 0.3 µg · kg<sup>-1</sup> · h<sup>-1</sup> + Lid 200 µg · kg<sup>-1</sup> · h<sup>-1</sup> (n = 6) or Mor 0.3 µg · kg<sup>-1</sup> · h<sup>-1</sup> + Lid 600 µg · kg<sup>-1</sup> · h<sup>-1</sup> (n = 6). Inside panels represent area under the curve (AUC) calculated from time-effect curve in intrathecal infusion for 6 days. Data are presented as mean ± SD. \*Significantly different from Mor 0.3. #Significantly different from Lid 200. \*\*Significantly different from Mor 0.3 + Lid 200.

However, the magnitude of morphine tolerance to visceral antinociception was less than that to somatic antinociception as indicated by greater %MPE in the CD test than in the TF test for the first 30 min in morphine challenge test after morphine infusion at 6 µg · kg<sup>-1</sup> · h<sup>-1</sup> or 10 µg · kg<sup>-1</sup> · h<sup>-1</sup> (fig. 1). However, as shown in the companion paper, the degree of antinociceptive effect in the visceral test was less than that in the somatic test. We therefore do not know if the increased tolerance is simply a result of less receptor occupancy, as discussed previously, in different development of tolerance to different type of nociceptive noxious stimulus.

As shown in the companion paper, the antinociceptive effects of intrathecal infusion of lidocaine gradu-

ally decreased, suggesting the development of tachyphylaxis.<sup>18</sup> The influence of coinfused opioid on tachyphylaxis of local anesthetic should be considered in clinical use of a combination of opioid and local anesthetic. The antinociceptive effects after the intrathecal coinfusion appeared as the total output, including interaction of morphine and lidocaine antinociception, modulated tolerance of morphine, and modulated tachyphylaxis of lidocaine. However, this study did not perform the lidocaine challenge test after completing the intrathecal infusion because we focused on the influence of coinfusion on the development of morphine tolerance and could not do two challenge tests at one time. As the next step, further studies on tachyphylaxis of local anesthetics are nec-

essary to establish the optimal doses for the combination of opioid and local anesthetics.

We conclude that the presence of lidocaine in combination with morphine to produce synergy does not reduce tolerance to morphine antinociceptive effects nor develop cross-tolerance. The continuous intrathecal infusion of morphine induced tolerance to somatic and visceral antinociceptive effects in a dose-dependent fashion.

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