Specific Enhancement by Fentanyl of the Effects of Intrathecal Bupivacaine on Nociceptive Afferent But Not on Sympathetic Efferent Pathways in Dogs

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Background: Bupivacaine alone, or in combination with opioids, has been shown to provide adequate pain relief without motor paralysis. This study examined the effects of bupivacaine administered intrathecally on sympathetic efferent and Aδ- and C-fiber-mediated afferent pathways in dogs and the interactions with intrathecal fentanyl.

Methods: Spontaneous activity in renal sympathetic nerves was observed, as were reflex somatosympathetic responses mediated by Aδ and C fibers evoked by supramaximal electrical stimulation of the tibial and radial nerve. Bupivacaine was administered intrathecally in doses of 0.5, 1, 2, and 3.5 mg, each in 0.5 ml, and 7 mg in 1 ml with or without pretreatment with 5.4 mg intrathecal fentanyl (ED₂₅ for depression of C tibial reflexes) in each of five preparations.

Results: Bupivacaine caused a dose-dependent inhibition of both Aδ- and C-fiber-mediated somatosympathetic responses evoked by tibial nerve stimulation. The depression of radial and tibial nerve reflexes and spontaneous renal sympathetic activity was similar. Pretreatment with fentanyl (5.4 μg, intrathecally) depressed tibial C-fiber reflexes by only 23.8% without any significant effect on either tibial Aδ or radial Aδ and C fiber responses. Fentanyl markedly enhanced the effect of subsequent doses of bupivacaine on tibial Aδ and C reflexes without any additional effect on either spontaneous sympathetic activity or radial responses.

Conclusions: Intrathecal bupivacaine has no selectivity for the afferent and efferent pathways, and intrathecal fentanyl acts synergistically to enhance the effect of bupivacaine on the afferent pathway without a measurable effect on sympathetic efferent pathways.

thetic outflow. (Key words: Analgesics, opioid: fentanyl. Anesthetic technique: intrathecal. Anesthetics, local: bupivacaine. Drug interaction: synergism.)

RECENTLY, clinical observations have shown that local anesthetics, in conjunction with opioids, administered spinally provide good analgesia to patients in labor with less intense motor blockade than that produced by local anesthetics alone.[1–4] Previous studies in animals indicated that opioids and local anesthetics administered spinally have a synergistic analgesic effect,[5–8] but that opioids do not enhance the motor blockade induced by the local anesthetics.[5,6]

Hypotension caused by sympathetic blockade can be another major unwanted effect of local anesthetics. Opioids do not cause significant depression of the efferent sympathetic pathway and motor function, but, administered alone, their analgesic efficacy is often inadequate compared with that provided by local anesthetics.[9]

Bupivacaine was the first local anesthetic that produced adequate pain relief in labor without a major effect on motor fibers.[10] However, the relative effect of bupivacaine on nociceptive afferent and sympathetic efferent pathways has not previously been fully studied, so that, for example, the degree of sympathetic blockade at a given level of sensory block is unknown.

This study investigated, first, whether bupivacaine administered intrathecally causes more sensory than sympathetic block; and, second, the combined action of fentanyl and bupivacaine on spontaneous sympathetic activity and sensory afferent and reflexly evoked efferent pathways of somatosympathetic responses in dogs.

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Materials and Methods

Experiments were performed on ten greyhound dogs weighing 20.4–25.3 kg (the study was approved by

Home Office). The animals were anesthetized with methohexital (15 mg/kg intravenously), followed by a bolus dose of 1% α-chloralose (30 mg/kg intravenously) and, thereafter, by infusion (17–20 mg·kg^{-1}·h^{-1} intravenously), and paralyzed with 10 mg succinylcholine every 20–30 min. After tracheal intubation, the lungs were ventilated (Harvard pump, Dover, MA) with oxygen-enriched air. The femoral artery and vein were cannulated. Esophageal temperature (Thermistor, Yellow Springs, OH), pHa, Pa_{O_2}, and Pa_{CO_2} (Radiometer ABL2, Emdrupvei, Copenhagen, Denmark) were kept within the ranges 37–39° C, 7.30–7.40, 170–210 mmHg, and 36–44 mmHg, respectively. The depth of anesthesia was monitored before each dose of succinylcholine (immobility, floppy ears, and absent responses to glabellar tap).

An intrathecal cannula (22G Y-can; Wallace, Colchester, Essex, UK) was inserted through the dura exposed *via* laminectomy at L1–2. A lateral superficial branch of the radial nerve in the left foreleg and the tibial nerve in the right hindleg were exposed. Single fascicles of the renal sympathetic nerves were retroperitoneally exposed close to the renal artery. All the nerves were desheathed, cut distally, and placed across silver electrodes in warm mineral oil.

The mean arterial pressure (MAP) was measured using calibrated strain gauges (Statham, Oxnard, CA) and displayed together with beat-by-beat heart rate (HR) using a heated stylus recording system (Devices M19, Welwyn Garden, Hertfordshire, UK). Repeated single (0.33 Hz) and higher frequency train (30 Hz) electrical stimuli of the same intensity (30 V) and duration (0.5 ms) were applied to the radial and tibial nerves using a Grass S88 Stimulator with a matched, directly coupled isolation unit (Grass 478A, Quincy, MA). The evoked responses in MAP and HR by repeated single and train stimuli were recorded and measured as the maximal effect. The stimuli were sustained up to 1 min and 10 s for repeated single and train stimuli, respectively, to allow the responses in MAP and HR to reach their maximal level. The MAP and HR were then allowed to return to the prestimulus control values, which required less than 1 min.

The efferent action potentials from renal sympathetic nerves were processed through a preamplifier and displayed on an oscilloscope (Tektronix 565, Beaverton, OR). To quantify the total spontaneous sympathetic activity at various stages of the experiments, 20-s samples were recorded, amplified, and subjected to full-wave rectification and integrated with an interval of

100 ms (Neurolog NL90, Welwyn Garden, Hertfordshire, UK), then digitized using a Gould system (1602, Ilford, Essex, UK). The evoked somatosympathetic responses in renal sympathetic nerves caused by repeated single supramaximal electrical stimulation (0.33 Hz, 30 V, 0.5 ms)[11] were averaged (16 responses), rectified, and integrated (Neurolog NL90). Both averaged and integrated signals were displayed on a pen recorder (Devices MX2).

The total electrical activity of the integrated signals of the spontaneous sympathetic activity (20-s samples) and the evoked somatosympathetic responses were measured (Gould 1602 system), recorded in arbitrary units, and expressed as percentage of control values. The evoked responses in renal sympathetic nerves during high-frequency train stimulation could not be recorded, because the repeated stimulus artifact was also recorded and interfered with the sympathetic signal.

Supramaximal electrical stimulation of any afferent nerve causes a mass discharge in the sympathetic nervous system that involves a supraspinal component, regardless of the site of stimulation in this particular model. Thus, for example, tibial and radial nerve stimulation cause similar reflexes because of activation of Aδ and C fibers in renal sympathetic nerves.[11] Therefore, the injection of drugs intrathecally at the level of the afferent input of the tibial nerve can demonstrate the effects of the drug on Aδ- and C-fiber afferent pathways. In addition, a study of the radial nerve reflexes may establish whether the drug also affects the efferent sympathetic pathway, because the small volume of drug administered limits its action near the site of injection, and cannot reach the level of the afferent input from the radial nerve. The protocol was selected to establish: (1) whether there is a selective effect of intrathecal bupivacaine on the afferent nociceptive compared with the efferent sympathetic pathways and (2) whether intrathecal fentanyl acts to enhance the effect of intrathecal bupivacaine specifically on either the afferent or the efferent pathways near the site of injection of the local anesthetic in the lumbar region.

Drugs used included: methohexital (Eli Lilly, Basingstoke, Hampshire, UK), α-chloralose (BDH Chemicals, Poole, Dorset, UK), succinylcholine (Wellcome, Crewe, Cheshire, UK), bupivacaine (Astra, Kings Langley, Herts, UK), fentanyl (Evans, Horsham, Sussex, UK), and naloxone (Sigma, Poole, Dorset, UK).

Bupivacaine was administered intrathecally in five preparations in incremental doses of 0.5, 1, 2, and 3.5 mg, each in 0.5 ml of physiologic saline (0.9%), and

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7 mg in 1 ml, at intervals of 25 min. These doses represent a concentration of 0.1, 0.2, 0.4, and 0.7%, respectively.

In an additional five preparations, a single dose of fentanyl 5.4 μg in 0.5 ml physiologic saline (0.9%) was administered intrathecally, and its effects were observed. This dose was calculated from previous data[12] as the approximate ED_{25} for blocking C fiber responses. Fifteen minutes later, the same incremental doses of bupivacaine were administered intrathecally at intervals of 25 min until both Aδ- and C-fiber-mediated somatosympathetic responses to tibial nerve stimulation were just abolished. Thirty minutes after the last dose of bupivacaine, 2 mg naloxone was administered intravenously.

Each data point was the mean of three measurements for the evoked somatosympathetic reflexes and the maximal increase in MAP and HR and five 20-s sample recordings for spontaneous sympathetic activity. A regression analysis was used to calculate the slope and 95% confidence intervals of the response curve using the computer program Statview + Graphic (Macintosh, Abacus Concepts, Berkeley, CA). The ED values for the depressive effect were calculated from the dose-response curves together with the 95% confidence intervals.[13] Statistical analysis was performed using ANOVA. Only if there was a significant difference between groups ($P < 0.05$) were paired t tests applied to compare appropriate data sets.

Results

Somatosympathetic Reflexes
Tibial Nerve Stimulation.

Bupivacaine Alone. Bupivacaine, administered intrathecally, produced dose-dependent inhibition of the Aδ- and C-fiber-mediated somatosympathetic reflexes (figs. 1 and 2). The Aδ and C reflexes were significantly depressed after 2 mg bupivacaine (0.4%), *i.e.*, total doses of 3.5 mg, and completely abolished after 7 mg (0.7%) intrathecally, *i.e.*, total doses of 14 mg. There were no significant differences between Aδ and C fiber reflexes after bupivacaine; however, when the dose increased to total doses of 3.5 and 7 mg intrathecally, the C fiber reflexes were inhibited to 53.4 and 25% of control values, while Aδ responses were decreased to only 68.9 and 41.8%, respectively (fig. 2). The $ED_{25,50,75}$ (95% confidence intervals), calculated from
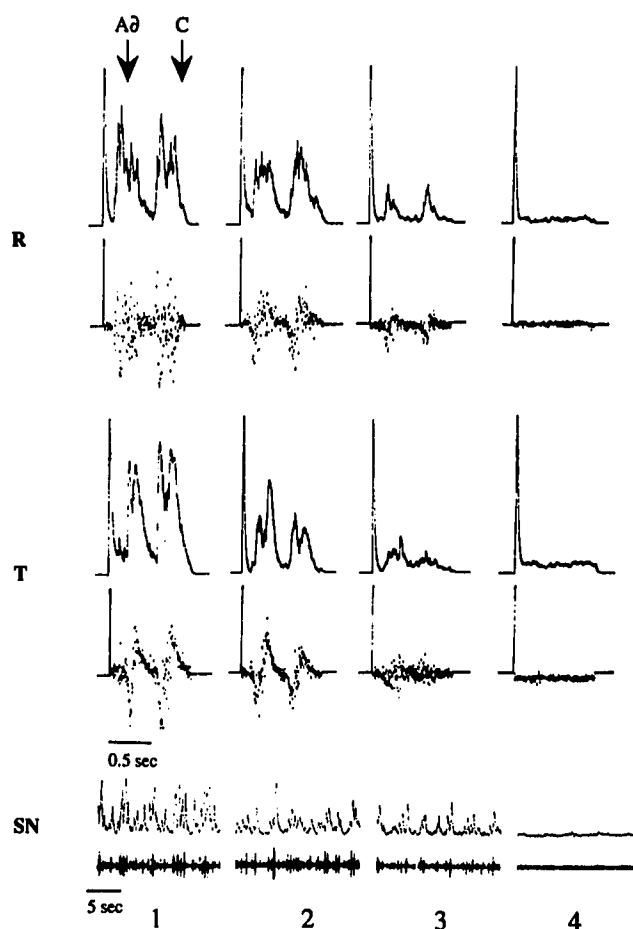

Fig. 1. The effects of intrathecal bupivacaine on the Aδ- (*i.e.*, early response) and C-fiber- (*i.e.*, late response) mediated somatosympathetic reflexes in a renal sympathetic nerve evoked by supramaximal electrical stimulation (0.33 Hz, 30 V, and 0.5 ms) of radial (R, *top*) and tibial (T, *middle*) nerves from one representative preparation (lower traces = the averaged transient of 16 responses; upper traces = rectified integral of the averaged signals). (*Bottom*) Effects on spontaneous renal sympathetic nerve activity (SN; lower traces = transient amplified signals; upper traces = integrated signals). Shown are (*left to right*): (1) control; (2) 10 min after 2 mg bupivacaine (0.4%), *i.e.*, total cumulative doses of 3.5 mg; (3) 10 min after a further dose of 3.5 mg (0.7%) bupivacaine, *i.e.*, total doses of 7 mg; and (4) 10 min after a further dose of 7 mg (0.7%) bupivacaine, *i.e.*, total doses of 14 mg.

the dose-response curves, for Aδ responses were 3.2 (2.3–3.8), 6.4 (5.6–7.4), and 9.6 (8.4–11.4) mg, respectively; for C reflexes, they were 2.2 (0.8–3.4), 5.2 (4–6.6), and 8.1 (6.6–10.6) mg, respectively. The Aδ/C ratios for $ED_{25,50,75}$ were 1.5, 1.2, and 1.2, respectively.

Fig. 2. The dose-related effects of intrathecal bupivacaine on Aδ- (closed circles and squares) and C-fiber- (open circles and squares) mediated somatosympathetic reflexes evoked by supramaximal electrical stimulation (0.33 Hz, 30 V, and 0.5 ms) of the radial nerve (top) and tibial nerve (bottom). Shown are bupivacaine alone (radial [A], tibial [C]) and after pretreatment with 5.4 μg intrathecal fentanyl (radial [B], tibial [D]). Percentage of control values is mean ± SD, n = 5. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, relative to control.
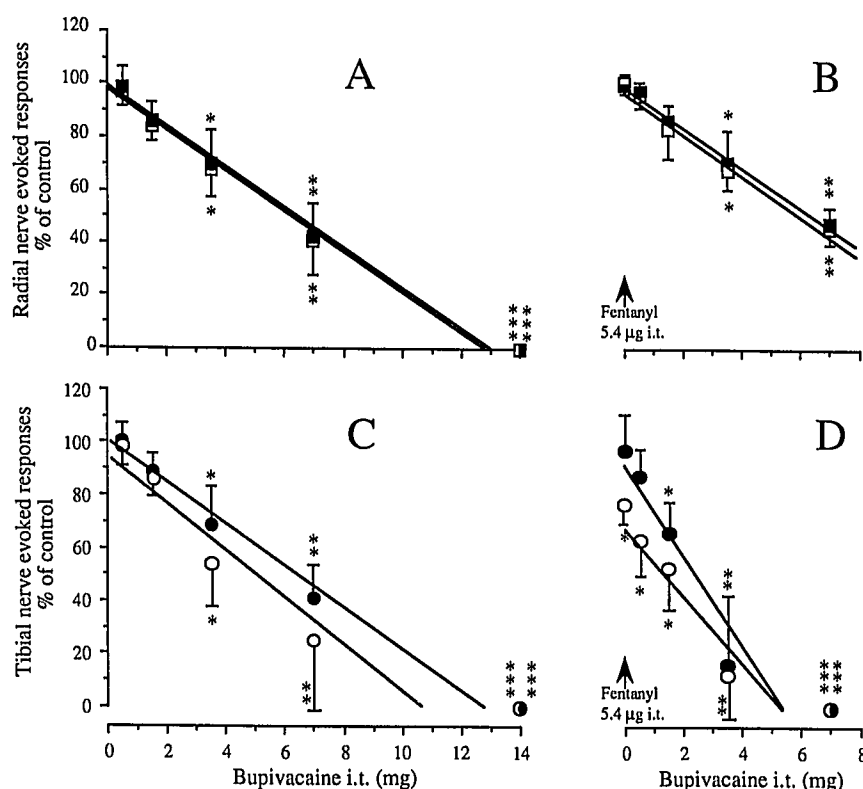
Pretreatment with Fentanyl. Fentanyl (5.4 μg intrathecally) inhibited the C-fiber-mediated responses to a mean value of 76.2% of control, and had no significant effect on Aδ reflexes. However, this small dose of fentanyl markedly reduced the subsequent doses of bupivacaine required to depress the Aδ and C reflexes, which were both abolished after total doses of bupivacaine between 3.5 and 7 mg (intrathecally), compared with 14 mg in the absence of fentanyl (figs. 2 and 3). The ED$_{25,50,75}$ (95% confidence intervals) for Aδ responses were 0.8 (−1.8), 2.4 (1.3–3.5), and 4 (3–6) mg, respectively. The ED$_{50,75}$ for C responses were 1.4 (−2.5), and 3.5 (2.5–5.9) mg, respectively. The predicted theoretical additive doses, calculated from the dose-response curves of bupivacaine, of ED$_{25,50,75}$ for Aδ responses were 2.9, 6.1, and 9.3 mg, respectively; and the ED$_{50,75}$ for C responses were 2.4 and 5.3 mg, respectively. Predicted/observed doses of ED$_{25,50,75}$ for Aδ responses were 3.6, 2.5, and 2.3, respectively; and the ED$_{50,75}$ for C were 1.7 and 1.5, respectively. The isobologram in figure 4 shows the degree of synergistic interaction for both Aδ and C reflexes between intrathecal fentanyl and intrathecal bupivacaine at the spinal level.

Radial Nerve Stimulation.

Bupivacaine Alone. The ED$_{25,50,75}$ for radial Aδ responses were 3.1 (2.5–3.8), 6.4 (5.6–7.3), and 9.7 (8.6–11.2) mg, respectively; and, for radial C responses, 3 (2.3–3.6), 6.2 (5.6–7.1), and 9.5 (8.5–10.8) mg, respectively. The effects of intrathecal bupivacaine on the Aδ- and C-fiber-mediated somatosympathetic reflexes evoked by stimulation of radial nerve and Aδ responses from the tibial nerve were similar (figs. 1 and 2).

Pretreatment with Fentanyl. After fentanyl (5.4 μg intrathecally), the subsequent doses of intrathecal bupivacaine depressed the radial Aδ and C reflexes significantly less than the responses from tibial nerve stimulation ($P < 0.05$). The radial responses were not affected by the pretreatment of fentanyl. When the tibial responses were completely abolished, the response to radial nerve stimulation still maintained about 50% of control values (figs. 2 and 3). The ED$_{25,50,75}$ for the radial nerve responses were 2.9 (2.2–3.6), 6.3 (5.3–5.7), and 9.6 (predicted) mg, respectively, for C-fiber responses; and 3.2 (2.6–4), 6.5 (5.5–8.2), and 9.8 (predicted) mg, respectively, for Aδ reflexes, which were similar to those for intrathecal bupivacaine alone.
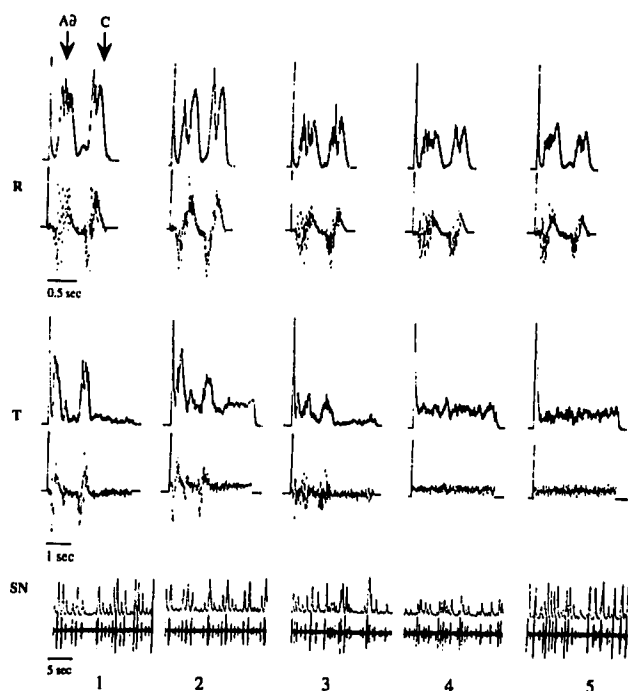
Fig. 3. The effects of intrathecal bupivacaine after pretreatment with fentanyl (5.4 μg, intrathecally) on the Aδ- (*i.e.*, early response) and C-fiber- (*i.e.*, late response) mediated somatosympathetic reflexes in a renal sympathetic nerve evoked by supramaximal electrical stimulation (0.33 Hz, 30 V, and 0.5 ms) of radial (R, *top*) and tibial (T, *middle*) nerves from one representative preparation (lower traces = the averaged transient of 16 responses; upper traces = rectified integral of the averaged signals). (*Bottom*) Effects on spontaneous renal sympathetic nerve activity (SN; lower traces = transient amplified signals; upper traces = integrated signals). Shown are (*left to right*): (1) control; (2) 5 min after 5.4 μg fentanyl (intrathecally); (3) 10 min after 2 mg bupivacaine (0.4%), *i.e.*, total doses of 3.5 mg (intrathecally); (4) 10 min after a further dose of 3.5 mg (0.7%) of bupivacaine, *i.e.*, total doses of 7 mg (intrathecally); and (5) 10 min after 2 mg naloxone (intravenously).

Spontaneous Renal Sympathetic Activity.

Bupivacaine Alone. Bupivacaine intrathecally also depressed and abolished the spontaneous sympathetic activity in parallel with the changes of Aδ and C reflexes from radial nerve stimulation (figs. 1 and 5).

Pretreatment with Fentanyl. Fentanyl (5.4 μg, intrathecally) had no significant effect on spontaneous sympathetic activity. The subsequent doses of intrathecal bupivacaine caused the same reduction of the spontaneous sympathetic activity as bupivacaine alone (figs. 3 and 5), and, again, the changes in the radial nerve evoked responses reflected changes in spontaneous sympathetic activity. When the tibial nerve

evoked somatosympathetic reflexes were abolished, the spontaneous sympathetic activity was still approximately 55% of control.

In summary, these results implied that fentanyl did not enhance the effect of intrathecal bupivacaine on the efferent sympathetic pathway, and indicated that there was a selective synergistic effect on the afferent nociceptive pathway between bupivacaine and fentanyl.

Evoked Responses in MAP and HR (fig. 6)

When the somatosympathetic responses evoked by repeated single stimulation (0.33 Hz) of tibial nerve were abolished by bupivacaine, the reflex increase in MAP and HR caused by both repeated single stimulation and high-frequency train stimulation (30 Hz) of the same intensity (30 V, 0.5 ms) applied to the tibial nerve were also entirely eliminated. In contrast, the responses to radial nerve stimulation showed only a small, but significant, reduction ($P < 05$). When bupivacaine pretreatment with fentanyl abolished the tibial somatosympathetic responses, it also blocked the reflex increase in MAP and HR caused by high- and low-frequency stimulation. However, the radial nerve-mediated responses in MAP and HR were maintained at control values (fig. 6).

The resting MAP and HR did not change significantly at any time during the study.

Naloxone (2 mg, intravenously) had no effect on the Aδ- and C-fiber-mediated somatosympathetic reflexes to both tibial and radial nerve stimulation; this was also true in one preparation in which the dose was increased to 5 mg (intravenously; fig. 3). However, the spontaneous renal sympathetic activity returned to 92.8% of the control values, which did not differ statistically.

Discussion

This study has clearly shown that bupivacaine administered intrathecally causes a similar dose-dependent inhibition of both Aδ- and C-fiber-mediated somatosympathetic reflexes, and, also, that there is no selectivity between its effect on the afferent and efferent pathways. In addition, intrathecal fentanyl selectively enhances the effects of intrathecal bupivacaine on the afferent nociceptive pathway, but without any effect on the efferent sympathetic pathway.

Dirksen *et al.* showed a dose-response relationship for the effect of intrathecal bupivacaine on rat with-
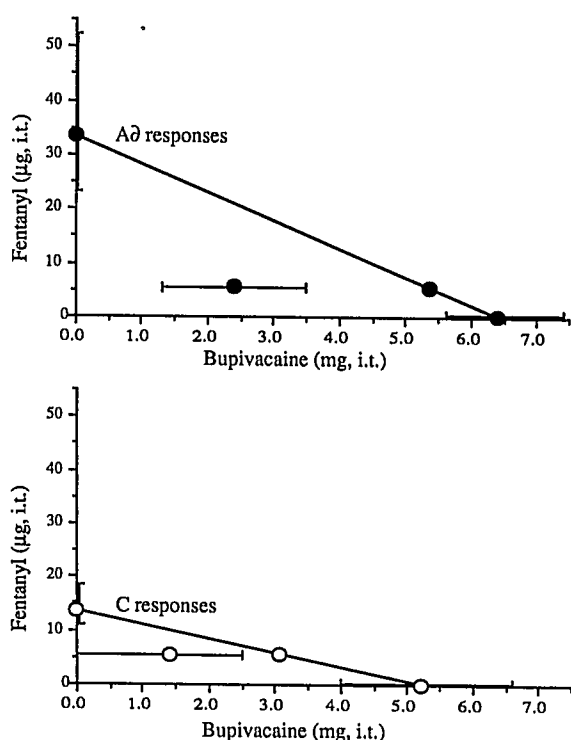
Fig. 4. The ED_{50} isobologram for the interaction of intrathecal fentanyl and bupivacaine on the Aδ- (top) and C-fiber- (bottom) mediated somatosympathetic responses caused by stimulation of the tibial nerve. The lines connecting the ED_{50} values (SD) of each drug are the additive lines. The points on the lines (closed and open circles) are the predicted doses of bupivacaine if its interaction with fentanyl were additive. The points below the left of the additive line are the dose (SD) of bupivacaine after fentanyl, and clearly indicate a synergistic effect.

fects in the spinal cord via different mechanisms. Opioid μ agonists open K^+ channels presynaptically to inhibit transmitter release and, thus, reduce Ca^{2+} influx, and have a direct postsynaptic effect, causing hyperpolarization and a reduction in neuronal activity.[15-17] It has also been suggested that opioids may affect Ca^{2+} flux directly.[18] Local anesthetics act mainly by blockade of voltage-gated Na^+ channels in the axonal membrane.[19] They may also have effects on synaptic transmission, i.e., a presynaptic inhibition of Ca^{2+} channels, in addition to their effects on nerve conduction.[19] Clearly, a combination of these effects may explain the observed synergism between local anesthetics and opioids, as originally suggested by Fraser et al.[7]

In addition to motor impairment, one of the major clinical concerns in the use of local anesthetics is sympathetic blockade. In this study, the depression of Aδ and C reflexes from radial nerve stimulation, acting through descending and efferent pathways, was similar to that of tibial responses. The dose-response curves for the effects of intrathecal bupivacaine on efferent sympathetic and afferent nociceptive pathways were similar. Thus, although selective block of the afferent pathway did not occur, it does imply that a partial blockade of both efferent and afferent transmission can be achieved using relative low doses and concentrations of local anesthetics. The addition of an opioid can then be used to exploit its synergistic action to complete the afferent block without increasing the regional local sympathetic blockade. This was demonstrated in the current study, which showed that when the opioid fentanyl was added to bupivacaine, the responses from radial nerve stimulation and the spontaneous sympathetic activity were maintained at approximately 55% of control, although the tibial responses were abolished; this indicates a selective enhancement by fentanyl of the effects of bupivacaine on the afferent pathway. Previous studies also indicate that opioids do not affect the motor blockade caused by local anesthetics.[5,6]

Opioids are generally less effective than local anesthetics for spinal analgesia in severe pain, e.g., during surgery and labor.[9] We found that opioids had a stimulation rate-dependent antinociceptive effect, i.e., opioids had no effect on high-frequency stimulation (30 Hz) at the dose that eliminated the nociceptive responses to low-frequency electrical stimulation (0.33 Hz) of the same intensity (30 V and 0.5 ms duration).[20] Local anesthetics are capable of totally blocking not only the responses to low-frequency stimulation, but also high-frequency train stimulation.[20] This is probably

drawal reflexes elicited by electrical stimulation.[14] However, this reflex could be related to motor impairment and, therefore, may not imply an antinociceptive effect. However, Fraser et al. also demonstrated that intrathecal lidocaine has a dose-dependent antinociceptive effect on spinal reflexes.[7] They found that lidocaine had a greater depressant effect on the Aδ- and C-fiber-mediated responses compared with reflexes mediated via large fiber (Aβ), but that this selective action only occurred at larger doses.

Opioids, combined with low concentrations of local anesthetics, have been used clinically to provide better analgesia while, at the same time, reducing unwanted side effects from either drug.[1-4] The results of this study demonstrate a synergism between the spinal antinociceptive effects of fentanyl and bupivacaine that is consistent with previous observations in rats and mice.[5-8] Opioids and local anesthetics have antinociceptive ef-
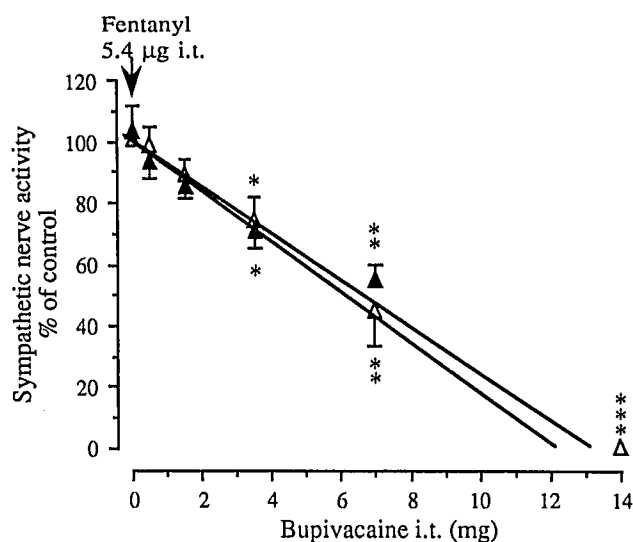
Fig. 5. The dose-related changes in spontaneous sympathetic activity in renal sympathetic nerves after intrathecally administered bupivacaine alone (open triangles) and after pretreatment with 5.4 μg intrathecal fentanyl (closed triangles), expressed as a percentage of control values (mean ± SD, n = 5). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, relative to control.

sponses did not change significantly. One hypothesis that may explain this phenomenon is that systemic naloxone reversed a descending baroreflex pathway activated either by the small dose of fentanyl or by modification of endogenous opioid activity during nociceptive stimulation. It has been suggested that naloxone, administered systemically, can facilitate C-fiber-mediated responses,[22] which may support this view. However, Tejwani et al. have shown that low concentrations of bupivacaine not only slightly inhibited the binding of naloxone, but also potentiated the displacement of
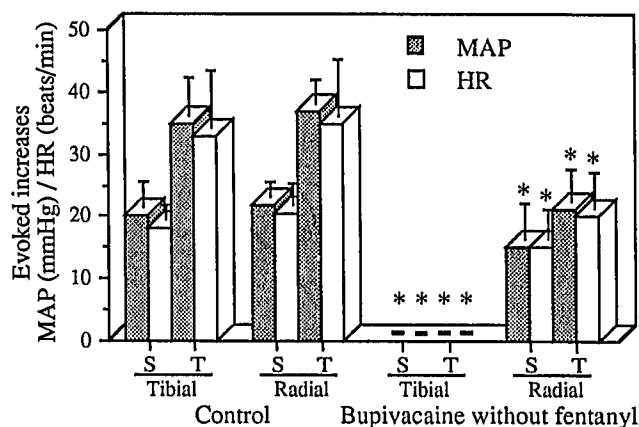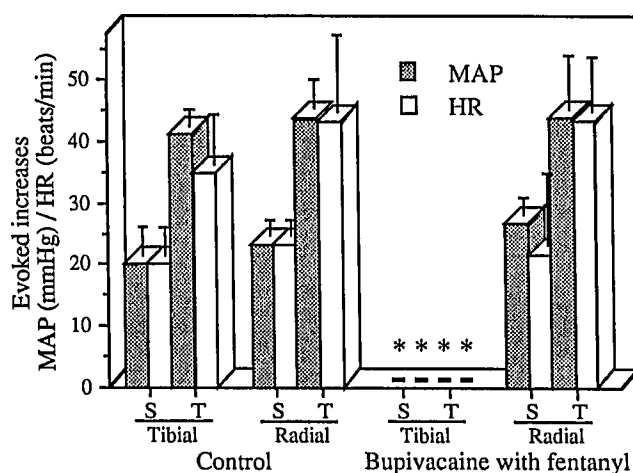
one of the reasons for the relatively inadequate analgesic effects of opioids when used alone. This study also showed that the evoked increase in MAP and HR to high-frequency train stimulation were eliminated by a relatively low dose of bupivacaine supplemented with fentanyl when it abolished the responses to repeated low-frequency stimulation. Previous studies indicated that local anesthetics also cause a frequency-dependent block in in vitro nerve preparations, i.e., if an in vitro nerve preparation is stimulated at a very low frequency and exposed to a low concentration of a local anesthetic, an increase in the stimulus frequency at the same concentration of the local anesthetic will increase the degree of block.[21] However, the precise implications of this phenomenon on the use of local anesthetics in clinical practice are by no means clear.

Naloxone had no effect on the Aδ- and C-fiber-mediated evoked responses when these were abolished with bupivacaine in animals pretreated with fentanyl (5.4 μg, intrathecally). However, it was administered over 2 h after fentanyl, the effects of which had declined, as shown by the reduction in the ratio of a predicated dose (theoretical additive dose) to the observed dose from the ED_{25} through ED_{75}. However, the spontaneous renal sympathetic activity was increased to the control level after naloxone, although the radial re-

Fig. 6. The effect of intrathecal bupivacaine with (top) and without (bottom) fentanyl (5.4 μg intrathecally) on evoked increases (mean ± SD, n = 5) in MAP and HR from nonstimulation control levels by repeated single (S; 0.33 Hz, 30 V, and 0.5 ms) and high-frequency trains (T) stimulation (30 Hz, 30 V, and 0.5 ms) applied to the tibial and radial nerves. The doses of bupivacaine just abolished Aδ- and C-fiber-mediated somatosympathetic reflexes to repeated single stimuli. *$P < 0.05$ compared with control.

naloxone by morphine. At high doses of bupivacaine, the binding of opioid ligands to all spinal receptors appears to be inhibited.[8] Therefore, although, at the start, there is synergism between the local anesthetic and opioid, the later administration of the opioid antagonist may not work because of modification of its binding properties by the local anesthetic. Moreover, we have found that a similar dose range of intravenously administered fentanyl was required to depress and abolish the tibial Aδ- and C-fiber-mediated somatosympathetic responses with or without pretreatment with an ED$_{30}$ of intrathecal bupivacaine (unpublished data); this would support the view that the properties of spinal opioid receptors may be modified by local anesthetics. Further work is required to establish whether this is a real phenomenon, because it would provide an alternative explanation for the ineffectiveness of naloxone in this study.

In conclusion, bupivacaine administered intrathecally depressed nociceptive reflexes in a dose-dependent manner. There was no selectivity on the nociceptive afferent and sympathetic efferent pathways. The effectiveness of spinal analgesia with bupivacaine can be enhanced if it is supplemented with fentanyl, which acts synergistically with the local anesthetic on the afferent pathway without causing any further inhibition of the efferent sympathetic activity.

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