A comparison of intrathecally administered narcotic and nonnarcotic analgesics for experimental chronic neuropathic pain

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The antinociceptive actions of morphine and tizanidine (an α₂-adrenergic agonist) administered intrathecally in a rat model of mononeuropathic pain were investigated. Tizanidine increased to normal levels the intensity of a noxious pressure stimulus required to induce paw withdrawal (p < 0.01) and decreased the duration of limb withdrawal from both normal-temperature and cooled floors in a dose-dependent manner (p < 0.01). Tizanidine had virtually no effect on the latency of paw withdrawal from a noxious heat stimulus. In comparison, morphine significantly decreased, in a dose-dependent manner, limb withdrawal from the normal-temperature and cooled floors and increased to cutoff values the withdrawal latencies of both noxious heat and pressure stimuli (p < 0.01). The effect of tizanidine was limited to the hyperalgesic limb and served to normalize reactive latencies, whereas morphine affected both hindlimbs and increased latencies to supranormal cutoff values. These data suggest that intrathecal tizanidine may be more specific than morphine in reversing the allodynia and hyperpathia associated with neuropathic pain states and may be of value in the management of patients with these clinical syndromes.

KEY WORDS • neuropathic pain • intrathecal administration • tizanidine • morphine • analgesia • allodynia • hyperpathia • rat
Materials and Methods

Two hundred eight male Sprague-Dawley rats weighing between 300 and 350 g were given 1 mg/kg atropine subcutaneously, anesthetized with 55 mg/kg sodium pentobarbital interperitoneally, and mounted in a stereotactic apparatus. Spinal catheterization was performed following the protocol of Yaksh and Rudy. At a catheter of PE-10 tubing was advanced 8.1 cm from the insertion site to the rostral margin of the lumbar enlargement, through a slit at the atlantooccipital membrane. The catheter was coated with silicon spray prior to insertion and was fastened to the skull with dental acrylic.

Pain Model

The common chronic neuropathic pain model used was that reported by Bennett and Xie. The common sciatic nerve was exposed at the level of the middle thigh by blunt dissection through the biceps femoris muscle. Four loose ligatures of 4-0 chromic gut suture were tied around the nerve at 1-mm intervals. The ligatures were tied so that they just constricted the surface of the nerve, as visualized under 40 magnification. The incision was then closed with 4-0 nylon sutures.

One week after surgery, baseline behavioral testing was performed on all animals, as outlined below. Thirty-five rats demonstrating signs of spinal cord injury or failing to demonstrate the typical neuropathic pain syndrome were excluded. After the baseline assessment, the animals randomly received an intrathecal bolus injection of either saline; 10, 20, or 30 \( \mu g \) morphine; or 10, 25, or 50 \( \mu g \) tizanidine in a 10-\( \mu l \) volume. These doses were based on prior studies documenting analgesia in nociceptive pain states without overt neurological toxicity (RM Levy, CV Dills, unpublished data). Thirty minutes after injection the pain tests were repeated.

Behavioral Tests

Behavioral testing to evaluate neuropathic pain included the following: 1) Spontaneous ambulation was used as a correlate measure of spontaneous pain; symptomatic animals raised their affected hindlimbs from the surface on which they were standing. The rats were placed on a flat surface maintained at room temperature and observed for a period of 20 minutes. The frequency and duration of spontaneous paw withdrawal from the floor were measured.

2) Cold floor ambulation was used as a correlate measure of alldynia; symptomatic animals raised their affected hindlimbs from the chilled surface on which they were standing. Rats were placed on a 1/8-in. thick aluminum floor chilled to 4°C by an underlying freezer. This temperature does not evoke pain-related responses from normal rats. An event recorder was used to measure the frequency and duration of paw withdrawal from the cold floor over a 20-minute period.

3) Paw pinch testing was used as a correlate measure of pressure hyperalgesia. Increasing pressure was gradually applied to the dorsal side of the affected hindpaw using a motor-driven device. The pressure (in grams) at which limb withdrawal occurred was recorded. Four measurements were taken at 3-minute intervals, so that each paw was tested every 6 minutes.

4) Noxious heat testing was used as a correlate measure of heat hyperalgesia. A radiant heat source was focused onto the proximal plantar hindpaw; the intensity of this heat source was calibrated to initiate limb withdrawal in normal animals with a mean latency of 4 seconds. The subsequent hindpaw withdrawal reflex interrupted a photocell and thus withdrawal latency was recorded. Four latency measurements were taken at 3-minute intervals, so that each paw was tested every 6 minutes.

For the pinch and heat tests, the effect of tizanidine or morphine was reported as the percentage of maximum possible effect (MPE). The pressure (in grams) at which limb withdrawal occurred was recorded. Four measurements were taken at 3-minute intervals, so that each paw was tested every 6 minutes.

Results

A dose-dependent increase in pinch-test paw withdrawal latency after intrathecal administration of morphine was seen in both affected and contralateral hindpaws (Fig. 1 left). Thirty micrograms of morphine increased the paw pinch withdrawal latency to greater than 99% of the MPE in both the affected and contralateral hindpaws (p < 0.001). Intrathecally administered tizanidine also increased paw pinch withdrawal latency in a dose-dependent manner, but only to a maximum of 19% (p < 0.01) and only in the affected hindpaw (Fig. 1 right). There was no effect of intrathecal administration tizanidine on the contralateral hindlimb.

Intrathecally administered morphine increased the heat-test paw withdrawal latency to a maximum of 98% of
the MPE in a dose-dependent manner in the contralateral hindpaw (P < 0.001; Fig. 2 left). In the affected paw intrathecal morphine increased the paw heat withdrawal latency to a lesser degree (29%; p < 0.01), largely due to decreased heat nociception in the affected limb. Intrathecally administered tizanidine had no effect on heat-test paw withdrawal latency in either hindpaw (Fig. 2 right).

Intrathecally administered morphine inhibited withdrawal of the affected limb from both the normal and cold floors during ambulation (Fig. 3); limb withdrawal during ambulation was essentially abolished in a dose-dependent manner (p < 0.001). Intrathecal tizanidine (25 µg) also nearly abolished withdrawal of the affected limb from the normal floor (p < 0.001; Fig. 4 left); withdrawal of the affected limb from the cold floor was inhibited in a dose-dependent manner to a maximum of 81% (p < 0.001; Fig. 4 right).

There was a significant effect of intrathecal morphine, but no effect of intrathecal tizanidine or saline on sham-operated or nonoperated control rats in the paw pinch, paw heat, and tail-flick tests (Table 1). The sham-operated and nonoperated rats exhibited no ambulation during predrug testing in the normal-floor and cold-floor tests.

**Discussion**

Both tizanidine and morphine administered intrathecally normalized abnormal ambulation, a phenomenon demonstrated only in the affected limb, in this animal model of chronic neuropathic pain. Intrathecal morphine increased the latency of withdrawal from noxious pressure to the cutoff (100% MPE) in both the affected and the contralateral paws in a dose-dependent manner. In contrast, tizanidine increased the latency of withdrawal from the noxious pressure stimulus to a maximum of 19% MPE in the affected hindpaw, a lesser analgesic effect than that of morphine. At the two higher doses of tizanidine, the withdrawal latency of the affected paw was approximately equivalent to the withdrawal latency of the contralateral paw.

This difference in effect between morphine and tizanidine on the latency of withdrawal from noxious pressure was the most significant result detected in the current

**FIG. 2.** Graphs showing mean percentage (± standard error of the mean) of maximum possible effect (MPE) for heat-test paw withdrawal latency after intrathecal administration of morphine (left) or tizanidine (right). Morphine produced a dose-dependent increase in the latency of the contralateral hindpaw and to a lesser degree the affected hindpaw. There was no effect of tizanidine at any dose. ** = p < 0.01; *** = p < 0.001.

**FIG. 3.** Graphs showing mean percentage (± standard error of the mean) of inhibition of ambulation for rats standing on a floor at room temperature (left) or at 4°C (right) after intrathecal administration of morphine. At both temperatures there was a dose-dependent decrease in ambulation in the affected hindpaw but no significant effect in the contralateral hindpaw, reflecting an absence of baseline spontaneous ambulation. ** = p < 0.01; *** = p < 0.001.

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study. Tizanidine has been shown to inhibit a number of spinal cord reflexes, and it has been suggested that the apparent analgesic effect of this agent is actually a reflection of nonspecific inhibition of some portion of the paw withdrawal reflex. Although morphine nonspecifically increased cutoff latency in both limbs, tizanidine prolonged withdrawal latency in the affected paw only, essentially not influencing the contralateral paw. In effect, tizanidine normalized the withdrawal latency of the affected limb. In that the tizanidine-induced increase in paw withdrawal latency was seen exclusively in the affected paw, the effect does not seem to be the result of generalized inhibition of spinal reflexes. Thus, tizanidine appears to specifically block the hyperalgesic mechanism underlying neuropathic pain but does not block baseline pain detection or spinal reflexes, whereas morphine apparently affects both normal and abnormal pain mechanisms.

Although testing withdrawal from a noxious heat stimulus initially suggested an analgesic effect of morphine on the contralateral limb but not on the affected limb, these data were skewed by the large number of animals in which the affected limb was apparently insensitive to heat. For a majority of the rats, the withdrawal latency of the affected paw reached cutoff during predrug testing; thus the MPE analysis was insensitive to any possible effect. By excluding from analysis those rats in which paw withdrawal latency reached cutoff during baseline noxious heat testing (Fig. 5), it became apparent that in animals at all sensitive to a heat stimulus, intrathecal morphine administration resulted in a dose-dependent increase in the latency of the response to noxious heat. At a dose of 30 μg morphine, the mean withdrawal latency reached cutoff values.

In contrast, tizanidine had no effect on the latency of withdrawal from a noxious heat stimulus of either the affected or the contralateral limb, even when animals insensitive to the heat stimulus on baseline testing were eliminated. These results further suggest that tizanidine is a more specific analgesic than morphine in neuropathic

![Graph showing mean percentage (± standard error of the mean) of inhibition of ambulation for rats standing on a floor at room temperature (left) or at 4 °C (right) after intrathecal administration of tizanidine. At both temperatures there was a dose-dependent decrease in ambulation in the affected hindpaw but no significant effect in the contralateral hindpaw, reflecting an absence of baseline spontaneous ambulation. * = p < 0.05; ** = p < 0.01; *** = p < 0.001.](image1)

![Graph showing mean percentage (± standard error of the mean) of maximum possible effect (MPE) for heat-test paw withdrawal latency after intrathecal administration of morphine, excluding animals in which latency reached cutoff during predrug testing. The dose-dependent increase in the affected hindpaw is similar to that in the contralateral hindpaw.](image2)

**TABLE 1**

*Maximum possible effect (MPE) of intrathecally administered saline, morphine, or tizanidine in three pain tests in sham-operated and nonoperated rats*

<table>
<thead>
<tr>
<th>Pain Test</th>
<th>Drug Administered</th>
<th>Saline</th>
<th>Morphine (30 μg)</th>
<th>Tizanidine (50 μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sham-operated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paw pinch</td>
<td></td>
<td>-0.7 ± 1.6</td>
<td>68.7 ± 12.5†</td>
<td>-1.3 ± 2.3</td>
</tr>
<tr>
<td>affected paw</td>
<td></td>
<td>0.0 ± 1.8</td>
<td>73.7 ± 13.6†</td>
<td>-3.6 ± 2.0</td>
</tr>
<tr>
<td>contralateral paw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paw heat</td>
<td></td>
<td>1.6 ± 2.5</td>
<td>52.3 ± 16.4‡</td>
<td>-0.1 ± 1.7</td>
</tr>
<tr>
<td>affected paw</td>
<td></td>
<td>2.5 ± 1.9</td>
<td>52.2 ± 13.9‡</td>
<td>0.1 ± 1.2</td>
</tr>
<tr>
<td>contralateral paw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonoperated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paw pinch</td>
<td></td>
<td>71.9 ± 14.6‡</td>
<td>-4.2 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>right paw</td>
<td></td>
<td>73.6 ± 14.3‡</td>
<td>-4.4 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>left paw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paw heat</td>
<td></td>
<td>66.8 ± 15.9†</td>
<td>-3.9 ± 2.4</td>
<td></td>
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<tr>
<td>right paw</td>
<td></td>
<td>62.6 ± 17.7†</td>
<td>-3.6 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>left paw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tail flick</td>
<td></td>
<td>-1.2 ± 7.8</td>
<td>74.0 ± 12.7‡</td>
<td>4.1 ± 2.0</td>
</tr>
</tbody>
</table>

* Data are presented as means ± standard error of the means of percent MPE. Statistical significance: † = p < 0.001, ‡ = p < 0.01.
pain states. Clinically, intrathecal tizanidine might well be a specific analgesic agent for the management of neuropathic pain. Because neuropathic pain states seldom include a major thermal component, normal thermal pain mechanisms may be preserved while clinically significant features of neuropathic pain, such as hyperalgesia and allodynia, might be alleviated.

Although McCarthy, et al.,9 reported that intrathecally administered tizanidine increased the latency of tail flick withdrawal in normal rats, in the current study intrathecal tizanidine had no effect on the latency of paw withdrawal form noxious pressure or noxious heat stimuli in either sham-operated or nonoperated rats. Although the mechanisms underlying normal tail flick and paw withdrawal may differ, the findings of McCarthy and coworkers appear to be at variance with our own. To address this question, we performed noxious heat-induced tail flick withdrawal latency testing in control rats. No effect of intrathecally administered tizanidine on tail flick withdrawal latency was observed. These results support our observation that intrathecal tizanidine specifically affects the mechanisms underlying neuropathic pain and not the mechanisms subserving normal pain transmission. The analgesic effect of intraspinally administered adrenergic agonists fits well with our current knowledge of descending central pain modulation pathways and their terminal noradrenergic projections.7 Noradrenergic fibers from the rostral ventral medulla descend in the dorsolateral funiculus of the spinal cord and project to cells that directly or indirectly regulate pain transmission. Stimulation of these projections inhibits pain transmission, as does the intraspinal administration of adrenergic agonists.11,12 The increased specificity of tizanidine as compared to morphine for neuropathic pain may be in part a function of the relative sites of action of these agents. Using intrathecally administered clonidine, for example, Ossipov, et al.,5 demonstrated an α2-adrenergic site of action clearly distal to that of morphine.

Conclusions

Both morphine and tizanidine administered intrathecally appear to be effective analgesics in this experimental mode of neuropathic pain. The degree of analgesia appears to be greater with morphine. However, the pattern of analgesia differs significantly between these two agents; morphine appears to be largely nonspecific, diffusely affecting all modalities, whereas tizanidine appears to be specific for pain perception in the region of neurological impairment and specific for those pathological mechanisms underlying allodynia and hyperpathia. Although clinical testing of intrathecal morphine for various pain states is currently in progress, the increased specificity of intrathecal tizanidine for neuropathic pain phenomena without affecting normal pain sensation suggest that it may be of significant utility in the treatment of chronic neuropathic pain states in humans.

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References


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