Assessment of the Potency and Intrinsic Activity of Systemic versus Intrathecal Opioids in Rats

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Background: One measure of an opioid’s efficacy is its ability to retain its analgesic effect as the intensity of a noxious stimulus is increased. A few studies have assessed the ability of either spinal or systemic opioids to produce analgesia using low- and high-intensity stimulation. There are little data available to show whether there are differences in efficacy between systemic and intrathecal opioid administration. The purpose of this study was to assess the relative efficacy of several clinically useful opioids systemically and spinal and to determine whether intrathecal administration resulted in greater efficacy than systemic administration.

Methods: Groups of rats were administered multiple doses of meperidine, morphine, hydromorphone, fentanyl, sufentanil, or buprenorphine either subcutaneously or intrathecally via implanted catheters. Noxious radiant heat was applied sequentially to each hindpaw, one at low intensity (adjusted to a mean withdrawal latency of 10 s) and one at high intensity (adjusted to a mean withdrawal latency of 3 s). Paw withdrawal latencies were recorded; dose–response curves for each intensity and each route of administration were graphically recorded, and ED₅₀ were calculated. Ratios of high-to-low-stimulus intensity ED₅₀ were calculated for both routes of administration for each drug, and the ratios of subcutaneous-to-intrathecal ED₅₀ for low-intensity stimulation were calculated to assess the relative systemic versus spinal potencies for each drug.

Results: The ratios of the high-to-low intensity ED₅₀ were meperidine, 11.8, morphine, 6.1, hydromorphone, 2.6, fentanyl, 2.3, sufentanil, 1.8, and buprenorphine, 24.0. For intrathecal administration, there was uniformity of the high-to-low-intensity ED₅₀ ratios for the agonist drugs (meperidine, 2.1; morphine, 2.1; hydromorphone, 1.9; fentanyl, 1.8; sufentanil, 1.6). For morphine and hydromorphone, the systemic ED₅₀ doses were several hundred times the intrathecal ED₅₀, whereas the systemic-to-spinal ED₅₀ ratios for the other drugs were 20 or less.

Conclusions: As intensity of noxious stimulation is increased, the more potent opioid agonists, administered systemically, produce antinociception with lesser increases in dose compared with lower potency drugs such as meperidine or morphine. When given spinally, all opioid agonists tested, including morphine and meperidine, demonstrated good efficacy, as measured by their ability to provide antinociception for high versus low intensity stimulation. (Key words: Opioids: systemic; intrathecal. Analgesia, intrinsic activity. Animal: rat.)

The use of opioids to control pain associated with metastatic cancer may be limited in some patients by the development of tolerance and by dramatic increases in the intensity of noxious stimuli as the size and number of metastatic lesions increases. There is evidence that increasing stimulus intensity is the more important factor because escalation in opioid dose has been shown to occur principally among patients who show new metastases or enlargement of existing lesions. It has been shown that, during experimental conditions of tolerance or increasing intensity of a noxious stimulus, certain opioids are more likely to produce complete or near-complete analgesia than others. In animal studies, more potent drugs are less affected by tolerance development or by increasing stimulus intensity. Drugs that are better able to maintain analgesic effects during conditions of tolerance or during intense nociceptor activation are those that require occupancy of a relatively small proportion of available receptors to produce effective analgesia. If a given drug, the fractional receptor occupancy (FRO), i.e., the proportion of receptors that must be occupied to produce a given effect, is high, the dose should be escalated markedly to maintain an effect as tolerance develops or as stimulus intensity increases. Such a drug may act as a partial agonist if the number of available functional receptors...
is insufficient to allow for a maximal effect. On the other hand, a drug that has a low FRO requirement may need only a small increase in dose to maintain a maximal effect during tolerance or high-stimulus intensity. Such a drug is said to have a high intrinsic activity.

The concept that certain drugs could produce a maximum effect while occupying a small proportion of receptors was initially proposed by Stephenson. This theory was confirmed independently by Furchgott and Nickerson, both of whom showed that pretreatment with irreversible receptor antagonists produced rightward shifts in agonist dose–response curves without depressing the maximum possible effect. These studies showed the fallacy of previous theories that maximum drug responses could only be achieved when 100% of receptors are occupied. More recently, the use of the irreversible μ-receptor antagonist B-fumaltrexamine (BFNA) has confirmed the concept that highly potent μ-opioid agonists, such as sufentanil, are less affected by reduction in availability of effective receptors than are less potent agonists, such as morphine. In this instance, there is a parallel between potency and efficacy.

Although several previous studies assessing the effect stimulus intensity on the analgesic effect of different opioids have used intrathecal drug administration, none have compared efficacy of systemic versus intrathecal administration. It has not been determined whether shifting from systemic to spinal administration provides more effective antinociception. This question is pertinent to the management of intractable cancer pain. In an attempt to answer this question, we examined the analgesic effect of systemic and intrathecal doses of several clinically important opioid analgesics using low- and high-intensity noxious thermal stimulation.

In general, the term drug efficacy refers to a drug's ability to produce a maximum possible effect (in the case of analgesics, pain relief or antinociception) at doses that produce tolerable side effects. Another measure of efficacy is the degree of rightward shift in the dose–response curve (or increase in the ED₅₀) as stimulus intensity is increased. There may be differences between two drugs using this measure even if both drugs are capable of producing a maximal effect at all stimulus intensities. It is this more subtle measure of efficacy that was investigated in this study.

**Methods**

These studies were carried out using a protocol approved by the Animal Research Facility of the Zablocki Veterans Administration Center (Milwaukee, Wisconsin). Male Sprague-Dawley rats weighing between 250 and 350 g were used.

**Injection Techniques**

For those animals given intrathecal drugs, lumbar intrathecal catheters were implanted via an incision in the atlantooccipital membrane during halothane anesthesia as previously described by Yaksh and Rudy. Catheters were advanced 11 cm caudally and externalized through the anterior portion of the scalp. Animals showing neurologic deficits on emergence from anesthesia were killed by barbiturate overdose. To ascertain correct placement of the catheters, 20 μl of 2% lidocaine was injected, followed by 10 μl saline, 0.9%, to flush the catheter 2–3 h after recovery from anesthesia. Only animals that developed transient bilateral motor and sensory blockade in the hind legs were included in the study. Intrathecal injection studies were carried out at least 5 days postoperatively. For animals given systemic opioids, drugs were dissolved in 0.3 ml normal saline and injected subcutaneously in the flank. Subcutaneous and intrathecal injections were blinded to the investigator performing analgesic testing.

**Testing Paradigm**

Response latency to noxious thermal stimulation of the hindpaw was assessed using a device similar to that previously reported by Hargreaves et al. Rats were confined in individual clear plastic cages placed on an elevated 2-mm thick glass surface. A movable radiant heat source (50 W, 8 V halogen projector lamp, Ushio, Tokyo, Japan) with a 4-mm aperture was situated below the glass surface. The chamber below the glass was thermostatically heated to maintain the glass temperature at 30°C. The radiant heat source was positioned to focus on that portion of the plantar surface of the hindpaw in contact with the glass. Activation of the radiant heat source initiated a timer. Intensities were calibrated to produce either a 5-s mean latency to brisk paw withdrawal (high intensity) or a 10-s mean latency (low intensity) in control animals. The high-intensity stimulus was used on the right hindpaw of each animal, whereas the low intensity was used on the left. For the low-intensity stimulus, if an animal failed to respond within a cut-off time of 20 s, the stimulus was terminated, and a latency of 20 s was recorded. Similarly, a cut-off time of 10 s was used for the high-intensity stimulus. These cut-off times were selected to minimize the incidence of thermal burns and to avoid subsequent thermal sensi-
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Figure 1. Dose–response curves for high versus low intensity noxious thermal stimulation for subcutaneous (upper panel) and intrathecal (lower panel, labeled IT) administration of meperidine, morphine, and buprenorphine. Higher subcutaneous doses of meperidine produced seizures and death in some animals. Higher intrathecal doses of buprenorphine were not tested because of drug insolvability.

...tization. Baseline measurements were recorded twice at each intensity, and the mean was calculated.

Four to seven animals were tested at each subcutaneous or intrathecal dose of sufentanil, fentanyl, hydromorphone, morphine, meperidine, and buprenorphine (four animals per group were used only when there was uniformly a maximal or minimal response). Individual animals were tested with no more than three doses of a given drug; trials were at least 72 h apart, and no animal received more than one drug. Doses were escalated until near-complete antinociception was achieved or until no further increase in effect was observed (plateau effect) or until adverse effects were observed. Analgesic testing was done at the time of peak analgesic effect for each drug and route of administration and ranged from 10 to 30 min after drug administration.

Behavioral Testing

The general behavior of all of the rats was carefully observed and tested. The following tests of motor function and coordination were carried out between 15 and 30 min after drug administration: observation of gait, righting reflex, and placing-stepping reflex (the dorsum of either hindpaw was drawn across the edge of a table, which normally results in the animal lifting the paw and placing it on the table surface).

Statistical Analysis

The %MPE for each test of response latency was calculated as:

\[
\text{postdrug latency} - \frac{\text{mean baseline latency}}{\text{cutoff time}} - \text{mean baseline latency} \times 100
\]

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Table 1. ED<sub>50</sub> (and 95% Confidence Intervals) for Subcutaneous (SC) and Intrathecal (IT) Drug Administration at High and Low Stimulus Intensities

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED&lt;sub&gt;50&lt;/sub&gt; SC (mg/kg)</th>
<th>Low Intensity</th>
<th>High Intensity</th>
<th>ED&lt;sub&gt;50&lt;/sub&gt; IT (mg/kg)</th>
<th>Low Intensity</th>
<th>High Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>2.55 (1.36–4.78)</td>
<td>30.18 (11.64–7.82)</td>
<td></td>
<td>0.13 (0.06–0.27)</td>
<td>0.27 (0.17–0.44)</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.36 (0.14–0.92)</td>
<td>2.20 (1.38–3.27)</td>
<td></td>
<td>0.8 (0.4–1.6)</td>
<td>1.6 (0.8–3.1)</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.11 (0.06–0.18)</td>
<td>0.28 (0.16–0.51)</td>
<td></td>
<td>0.2 (0.1–0.5)</td>
<td>0.4 (0.2–0.8)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>15 (10–22)</td>
<td>32 (24–44)</td>
<td></td>
<td>0.9 (0.4–2.0)</td>
<td>1.8 (0.7–4.8)</td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>3.1 (1.8–5.4)</td>
<td>5.6 (4.3–7.2)</td>
<td></td>
<td>0.3 (0.08–1.3)</td>
<td>0.54 (0.21–1.34)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>16 (7–36)</td>
<td>152†</td>
<td></td>
<td>8.8 (2.7–28.2)</td>
<td>†</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mg/kg except for those values marked with †, which are expressed as µg/kg.
† 95% Confidence intervals could not be calculated.
‡ ED<sub>50</sub> could not be calculated.

The ED<sub>50</sub> values and 95% confidence intervals for individual drugs and drug combinations were calculated using the pharmacologic software programs of Tallarida and Murray. The ratios of the ED<sub>50</sub> values for high intensity versus low intensity stimulation were compared for subcutaneous and intrathecal administration for each drug. In addition, to compare the intrathecal to the subcutaneous potency for each drug, the intrathecal and subcutaneous ED<sub>50</sub> values for low-intensity stimulation were compared, and the ratios of these values were recorded. The 95% confidence intervals for the dose ratios were calculated according to the method described by Tallarida and Murray.  

Results

Subcutaneous Administration

For meperidine, morphine, and fentanyl, there was a significant difference between ED<sub>50</sub> values for high- versus low-intensity stimulation. The lower potency opioids, meperidine and morphine, required greater dose escalation (i.e., rightward shift in dose response curve) to produce analgesia for the higher intensity stimulus, whereas the higher potency drugs, hydromorphone, fentanyl, and sufentanil, required little dose escalation by comparison. At the highest dose of meperidine tested, 50 mg/kg, maximum analgesia for the high-intensity stimulus was not achieved. Higher doses produced seizures and death in most animals. There was a significant difference in high-to-low intensity dose ratios for meperidine versus fentanyl and meperidine versus sufentanil. There was overlap of 95% confidence limits for all of the other drug combinations. The dose–response curves are shown in figures 1 and 2, and the ED<sub>50</sub> values and 95% confidence intervals for high- versus low-intensity stimuli are shown in table 1. The ratios of high- to low-intensity ED<sub>50</sub> values and the confidence intervals for the dose ratios are shown in table 2.

For subcutaneous buprenorphine, maximal analgesia was achieved for the low-intensity stimulus but not for the high-intensity stimulus. Increasing the dose beyond 300 µg/kg failed to produce a greater analgesic effect. In other words, there was a ceiling effect. The dose–response curve for subcutaneous buprenorphine is shown in figure 1, and the ED<sub>50</sub> values are shown in table 1. The confidence intervals for the ED<sub>50</sub> for the high-intensity stimulus could not be calculated accurately because few values above 50% efficacy were achieved.

There were some mild behavioral changes noted with some of the drugs tested. There was mild sedation with 20 mg/kg morphine and mild rigidity and catatonia at 100 µg/kg fentanyl and 30 µg/kg sufentanil. These animals remained immobile, often in uncharacteristic postures, when left alone, but they resumed more normal activity and posture when handled. Meperidine at a dose of 100 mg/kg produced seizures in 3 of 4 animals and death in 2 of 4 animals. This generally occurred after a 10 to 20 min delay. No behavioral abnormalities were observed at lower doses.

Intrathecal Administration

For administration of meperidine and morphine, there was a substantial difference in the drugs' ability to produce analgesia for high-intensity stimulation compared with the results for systemic administration. For both drugs, there was only a small rightward shift in ED<sub>50</sub> with the high-stimulus intensity. The high- to low-inten-
Table 2. Ratios of High to Low Intensity Stimulation ED_{95} for Subcutaneous (SC) and Intrathecal (IT) Drug Administration, and Ratios of Subcutaneous to Intrathecal ED_{95} for Low Intensity Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Ratio SC High/ Low ED_{95}</th>
<th>CI</th>
<th>Ratio IT High/Low ED_{95}</th>
<th>CI</th>
<th>Ratio SC/IT ED_{95} (Low)</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>11.8</td>
<td>(4.3–32.8)</td>
<td>2.1</td>
<td>(1.2–3.5)</td>
<td>19.3</td>
<td>(7.3–51.0)</td>
</tr>
<tr>
<td>Morphine</td>
<td>6.1</td>
<td>(2.4–15.6)</td>
<td>2.1</td>
<td>(0.8–5.6)</td>
<td>450</td>
<td>(140–1443)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2.6</td>
<td>(1.2–5.7)</td>
<td>1.9</td>
<td>(0.8–4.2)</td>
<td>540</td>
<td>(224–1299)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2.3</td>
<td>(1.2–4.2)</td>
<td>1.8</td>
<td>(0.7–4.8)</td>
<td>16.6</td>
<td>(6.7–41.2)</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1.8</td>
<td>(1.0–3.2)</td>
<td>1.6</td>
<td>(0.3–9.0)</td>
<td>9.4</td>
<td>(2.1–42.9)</td>
</tr>
</tbody>
</table>

Values in parentheses are the calculated 95% confidence intervals (CI) for the dose ratios.

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ity ED_{95} ratio for intrathecal meperidine was 2.1 (compared with 11.8 for subcutaneous administration) and for morphine was 2.1 (compared with 6.1 for subcutaneous morphine). The difference between dose ratios for intrathecal versus subcutaneous administration was only significant for meperidine. At all doses of intrathecal meperidine that showed an analgesic effect, there was at least some degree of motor blockade, suggesting a local anesthetic effect. No behavioral abnormalities were evident after intrathecal administration of any of

Figure 2. Dose–response curves for high versus low intensity noxious thermal stimulation for subcutaneous (upper panel) and intrathecal (lower panel, labeled IT) administration of hydromorphone, fentanyl, and sufentanil.

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the other drugs. For intrathecal hydromorphone, fentanyl, and sufentanil, the ED<sub>50</sub> ratios for high- versus low-intensity stimulus were similar to the ratios seen for subcutaneous administration. Differences between ED<sub>50</sub>s for high- versus low-intensity stimulation after intrathecal drug administration were not significant for any of the drugs tested. The dose–response curves for intrathecal administration of these drugs are shown in figures 1 and 2; the ED<sub>50</sub>s and 95% confidence intervals are shown in table 1, and the ED<sub>50</sub> ratios and 95% confidence intervals are shown in table 2.

Because of the relative insolubility of buprenorphine, doses above 50 μg/kg could not be given. At this dose, there was a partial analgesic effect for low-intensity stimulation, and there was no effect for the high-intensity stimulus. The intrathecal dose–response curves are shown in figure 1.

When the intrathecal and subcutaneous ED<sub>50</sub>s for low-intensity stimulation were compared for each drug as a measure of the relative systemic and spinal potencies, there was relatively little difference for meperidine, fentanyl, sufentanil, or buprenorphine. The 95% confidence intervals of intrathecal and subcutaneous ED<sub>50</sub>s overlapped for all of these drugs (see table 1). By contrast, there was a more than 400-fold greater potency with intrathecal administration for morphine and hydromorphone, with no overlap of the 95% confidence intervals. The subcutaneous-to-intrathecal dose ratios for these two drugs differed significantly from the dose ratios for hydromorphone, fentanyl, and sufentanil.

**Discussion**

Previous studies have shown rightward shifts of dose–response curves for systemic opioids as stimulus intensity is increased. Anker<sup>16</sup> reported a threefold increase in the ED<sub>50</sub> for subcutaneous morphine in rats when hotplate temperature was increased from 50 to 55°C and a fivefold increase when temperature was increased to 59°C. There was a 12-fold increase in the ED<sub>50</sub> for subcutaneous pentazocine when hotplate temperature was increased from 50 to 55°C, and at 59°C, there was no apparent analgesic effect. These data are similar to our results for subcutaneous morphine and buprenorphine. Granat and Saemles<sup>17</sup> examined the effect of increasing intensity of noxious thermal stimulus on ED<sub>50</sub>s of several orally administered opioids in mice. They found a greater escalation in dose requirements for low potency drugs (codeine, meperidine, and propoxyphene) than for higher potency drugs (methadone and levorphanol).

The present study documents better efficacy with systemic administration for the more potent drugs, hydromorphone, fentanyl, and sufentanil, in producing antinociception with an intense stimulus. These results provide a theoretic rationale for changing from morphine to sufentanil for severe, unrelieved cancer or posttraumatic pain.

Under the conditions of this study, meperidine was incapable of producing complete analgesia for the more intense stimulus and acted as a partial agonist. Higher doses were not tolerated, resulting in seizures and death. This result, coupled with the fact that meperidine is metabolized to a toxic metabolite, suggests that it is a poor choice for the management of severe cancer-related pain.

When meperidine and morphine were given intrathecally, there was less difference between high and low intensity ED<sub>50</sub>s. For intrathecal meperidine, the ratio of the high-to-low ED<sub>50</sub> was 2.1 compared with 11.8 for systemic meperidine. However, there was a qualitative difference in the effect of the drug when given intrathecally. At least some degree of hindlimb motor dysfunction was noted at all doses that produced analgesia, suggesting that the difference in behavior associated with intrathecal meperidine was related to its local anesthetic effect. On the other hand, intrathecal morphine showed a much lower high-to-low intensity ED<sub>50</sub> ratio without producing any apparent behavioral changes other than increased response latency. We postulate that the apparent improvement in efficacy may be related to a more intense spinal opioid effect of the intrathecal morphine. For hydromorphone, fentanyl, and sufentanil, there was little difference in ED<sub>50</sub> ratios for intrathecal compared with subcutaneous drug administration.

There is substantial experimental evidence that intrathecal morphine produces different effects than systemic morphine. Spinally administered opioids are known to produce significant dose-dependent analgesia by action on the spinal cord dorsal horn. The analgesic effect of opioids in the cord is related to the presynaptic inhibition of the release of neurotransmitters from small primary afferents<sup>18–20</sup> and to hyperpolarization of postsynaptic neurons produced by opening of K<sup>+</sup> channels.<sup>18</sup> The mechanism of action of systemically administered opioids is more complex. Even in doses that produce profound analgesia, they do not appear to exert substantial spinal effects.<sup>21–25</sup> It would appear from our

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data that there is little difference in efficacy between intrathecal and systemic routes of administration for hydromorphone, fentanyl, or sufentanil. Unlike morphine, there is little published information regarding spinal versus supraspinal actions of these drugs when administered systemically. If they have a substantial spinal mechanism when administered systemically, this may explain the lack of difference in efficacy between the two routes of administration.

These data differ somewhat from other studies comparing the ED_{50} ratios of high- to low-intensity thermal stimulation after administration of intrathecal opioids. Saeki and Yaksh\textsuperscript{24} found that increasing the bath temperature from 52°C to 60°C produced a 3.7-fold increase in ED_{50} for the tail immersion test with intrathecal morphine but no right shift for intrathecal sufentanil. Dirig and Yaksh\textsuperscript{24} using a the Hargreaves device and a paradigm similar to ours, found much greater rightward shifts for intrathecal morphine than for intrathecal sufentanil, indicating that there may be some therapeutic benefit in changing from intrathecal morphine to intrathecal sufentanil. That study differs from ours in that it used a 20-s cut-off time rather than 10 s for the high-intensity stimulus, producing a more intense and potentially more tissue damaging stimulus. The high-intensity stimulus used in our study may not have been sufficient to reveal the differences seen other studies.

There was considerable variation in the ratios of systemic-to-intrathecal ED_{50} of the drugs tested. Morphine and hydromorphone were several hundred times more potent intrathecally than subcutaneously, whereas there were relatively small differences in these dose ratios for meperidine, fentanyl, and sufentanil. The intrathecal-to-subcutaneous dose ratios we reported bear a striking resemblance to the ratios of intracerebroventricular (ICV) to intravenous analgesic doses in rabbits reported by Herz and Teschemacher\textsuperscript{25} in 1971. They determined the dose producing the maximum effect by each route for a number of opioids and found that the intravenous-to-ICV dose ratios were morphine, 892, hydromorphone, 531, meperidine, 8.5, and fentanyl, 5.8. They found a high degree of correlation between the lipid solubility of each drug and the intravenous-to-ICV dose ratios. They postulated that hydrophilic drugs, such as morphine and hydromorphone, remain for long periods of time in the cerebrospinal fluid, maintaining a concentration gradient from the ventricles to the brain. Lipid-soluble drugs diffuse rapidly from the cerebrospinal fluid to the brain, but they diffuse equally rapidly from the brain to the blood vessels. There is rapid equilibration from the cerebrospinal fluid to the intravascular compartment, thus minimizing the differences between ICV and intravenous effects. Similar explanations are likely to hold true for the transfer of drugs from the spinal subarachnoid space to the spinal cord.

**Clinical Correlations**

If these data are pertinent to clinical situations, it may be advantageous to change from systemic meperidine and possibly morphine to systemic hydromorphone, fentanyl, or sufentanil. Similarly, it might be reasonable to change from systemic morphine to intrathecal morphine administration. Likewise, intrathecal meperidine may provide better analgesia than systemic meperidine, particularly in light of its local anesthetic effect. Such postulates remain to be borne out in clinical trials.

There have been a few reports of reductions in pain and improvements in side effects associated with conversion from systemic to intrathecal administration of morphine for cancer and chronic pain,\textsuperscript{26-28} but most of these reports are descriptive and fail to show objective changes in pain intensity or reduction in side effects. It is evident that intrathecal morphine alone is often inadequate to provide effective relief for intractable cancer pain, and several recent studies of chronic intrathecal opioids for cancer pain use a combination of morphine and bupivacaine.\textsuperscript{29,30}

**Conclusions**

Using the model of analgesic testing at different stimulus intensities, there appears to be some correlation between potency and efficacy (as defined by a drug’s relative ability to provide analgesia of a high-intensity stimulus) for systemically administered opioid agonists. This relationship could not be verified after intrathecal administration.

**References**


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