

## Spinal Sufentanil Effects on Spinal Pain-transmission Neurons in Cats

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The ability of sufentanil to suppress noxiously evoked activity of wide dynamic range (WDR) neurons was studied in decerebrate, spinal-cord-transected cats. Sufentanil, 2.5  $\mu\text{g}$  ( $n = 7$ ) or 5.0  $\mu\text{g}$  ( $n = 7$ ), when administered spinally, produced a significant, dose-dependent suppression of noxiously evoked ( $51^\circ\text{C}$  radiant heat stimulus) activity of WDR neurons in the dorsal horn of the spinal cord. Spontaneous recovery from sufentanil suppression was not seen for up to 2 h. Reversal following intravenous naloxone, 0.12 mg, although present, was not as complete as that seen following other spinal opiates. Intravenous sufentanil, 5.0  $\mu\text{g}/\text{kg}$  ( $n = 4$ ), produced significant but short-lasting depression of noxiously evoked WDR neuron activity. A comparison of the results of this study with data from a previous fentanyl study suggests that sufentanil may be more appropriate than fentanyl for spinal or epidural administration because of a possible longer duration of action. However, the lesser degree of naloxone reversal seen in this study may suggest that, clinically, reversal of sufentanil effects may be more difficult. (Key words: Analgesics: sufentanil. Anesthetic techniques: spinal narcotics. Spinal cord: neurons, WDR.)

THE DEMONSTRATION THAT the administration of opiates near the spinal cord produced a potent antinociceptive action that was of long duration, intense, initially segmental, and free of sympathetic, motor, or proprioceptive effects was an exciting development in pain control.<sup>1-3</sup> One of the most frequently reported agents used for spinal opiate analgesia is morphine. Its dramatic pain relief, however, frequently is accompanied by unwanted side effects (most importantly, late respiratory depression). This complication is felt to arise from rostral spread of morphine in cerebrospinal fluid (CSF). It is felt that its low lipid solubility results in less drug getting into the neural tissue and, thus, more remaining in the CSF with a resulting increase in the chance of respiratory depression.<sup>3</sup> It has been proposed that more lipid soluble agents may be less likely to produce respiratory depression of late onset.<sup>4</sup>

Fentanyl, a drug with greater lipid solubility than morphine, has been used successfully for spinal (epidural) opioid analgesia, but its duration of action has been predictably shorter than that of morphine.<sup>5</sup> Sufentanil, a

synthetic narcotic similar to fentanyl, may be a more appropriate drug for spinal opioid analgesia because, although its lipid solubility is slightly less than that of fentanyl,<sup>6</sup> it dissociates more slowly than fentanyl from opiate receptors,<sup>6</sup> is more potent than fentanyl,<sup>7</sup> and has a higher therapeutic index than does fentanyl.<sup>7</sup> These differences may decrease the likelihood of untoward side effects when sufentanil is used for spinal opioid analgesia.

This study, the last in a series in which the effects of fentanyl analogues on spinal neuronal activity were studied, examined the ability of spinally administered sufentanil to block noxiously evoked activity of wide dynamic range (WDR) neurons in the spinal cord. We were particularly interested in comparing dose-response relationship, time of onset, duration of drug effects, and naloxone reversibility of any observed effects with previously determined effects of fentanyl in the same model. In addition, we wanted to compare the difference in onset of effects following spinal *versus* iv sufentanil administration when comparable levels of neuronal suppression were produced. Since equipotency has not been determined for spinal opiates, we used, as an endpoint for comparison, the ability of the drugs to produce comparable levels of depression of noxiously evoked activity of dorsal horn WDR neurons.

### Methods and Materials

All institutional, state, and federal guidelines for the care and use of experimental animals were observed during all parts of this study. Eighteen cats of either sex, weighing 2.3–4.0 kg, were used in this study. Surgical preparation was carried out under halothane–nitrous oxide–oxygen anesthesia. Following the placement of an external jugular vein catheter for fluid administration and a carotid artery catheter for direct blood pressure monitoring, a tracheotomy was performed. The animals were paralyzed with gallamine and mechanically ventilated. Decerebration was produced by bilateral electrolytic lesions in the midbrain reticular formation; the spinal cord was transected at the T-12 level; and anesthesia was discontinued. Animals were maintained for the remainder of the experiment on 100%  $\text{O}_2$ .

End-tidal carbon dioxide tension ( $\text{PETCO}_2$ ) was monitored and maintained at 3.5–4%. Body temperature also was monitored and maintained within normal limits by a

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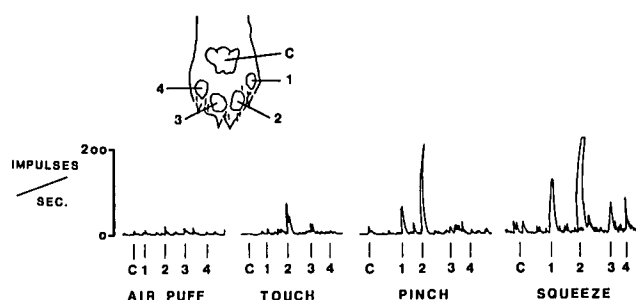


FIG. 1. A typical response pattern of a WDR neuron is shown. Each of the bottom panels represents the evoked responses of the neuron when the indicated stimulus was applied to the pads on the animal's foot (pad location is indicated by the letter C or numbers 1 through 4). The most sensitive part of the receptive field was located on pad number 2 of the cat's paw. As the intensity of stimulation increased from air puff on the receptive field to squeezing of the receptive field, the evoked activity (impulses/s) increased as well. The squeezing stimulus was judged to be noxious when applied to the skin of the experimenter.

thermostatically controlled heating pad and heat lamp. Systolic blood pressure was maintained over 100 mmHg throughout the experiment. A laminectomy was performed at L-4 through L-6, exposing the lumbar spinal cord. The dura was incised and reflected, and the spinal cord was covered by 37° C normal saline. A tungsten microelectrode with 9–12 Mohm impedance was advanced slowly into the spinal cord to record neuronal activity extracellularly from single WDR neurons that had their receptive fields on the foot pads of the hindpaw. WDR neurons were identified by their evoked response to peripheral stimuli of the following type: 1) air puff, 2) light touch with a camel hair brush, 3) pinch with forceps, 4) squeezing with forceps, and 5) noxious radiant heat (51° C).

Following the isolation of a single cell and control studies (only one neuron was studied per animal), the normal saline that had been bathing the spinal cord was removed, and sufentanil, either 2.5  $\mu$ g ( $n = 7$ ) or 5.0  $\mu$ g ( $n = 7$ ), dissolved in 0.5 ml of normal saline was applied gently onto the spinal cord (only one dose of sufentanil was studied per animal). In several experiments, naloxone (0.12 mg) was injected intravenously 31 min after spinal sufentanil administration. In another series of experiments ( $n = 4$ ), 5.0  $\mu$ g/kg of sufentanil was administered intravenously.

The doses of sufentanil used in this study were chosen so that comparisons could be made with previous work done in this laboratory using the same model. In particular, we wanted to compare the effect of sufentanil with previously reported effects of fentanyl. A direct comparison of the effects of spinally administered opiates is not possible because the potency ratios are not known pre-

cisely for spinal administration. We attempted to overcome that problem by using a similar endpoint for the drug effect (comparable, but not maximum, levels of depression of neuronal activity). The doses of spinal sufentanil used in this study produced levels of maximum neuronal suppression that were comparable to those previously reported for other spinally administered opiates using the same model.<sup>7,8</sup>

Spontaneous and evoked activity were recorded during control studies and following spinal or intravenous drug administration. Evoked activity was elicited every 3 min by the application of an 8-s, 51° C radiant heat stimulus to the center of the neuron's receptive field on the foot pad. In those experiments in which naloxone was not used, activity was recorded for as long as possible (recordings were terminated when single cell isolation became inadequate).

All data were collected on-line and analyzed by a PDP 11/40 computer. In addition, polygraph recordings were made of the skin temperature, the integrated neuronal activity, and blood pressure. As recommended by a consulting statistician, Student's *t* test was used for determination of statistical significance. Two things were done to avoid the problem of repeated *t* tests (increased alpha, type I error). Only *P* values of 0.01, rather than 0.05, were considered significant, and tests were only performed on the 3- and 30-min time points. These steps assured that the type I error would be no greater than if ANOVA and appropriate *post hoc* comparisons were used.

## Results

All of the neurons (18) included in this study were of the WDR type. Figure 1 shows a typical response pattern of a WDR neuron to natural stimuli. WDR neurons increase their firing rate as the intensity of stimulation increases, until they reach a maximum firing rate when noxious intensities are used.

### SPINAL ADMINISTRATION

The noxiously evoked activity of all WDR neurons studied was suppressed by spinally administered sufentanil. Figure 2 shows the effects of sufentanil on two separate WDR neurons. The noxiously evoked activity of each neuron was suppressed by spinal sufentanil. The 5.0  $\mu$ g dose produced greater suppression at 30 min (reduction to 28% of control) than did the 2.5  $\mu$ g dose (reduction to 62% of control).

Figure 3 shows the effect of sufentanil (2.5  $\mu$ g and 5  $\mu$ g) on the mean noxiously evoked activity of all the WDR neurons on which the effects of spinal application was

examined. Significant suppression was observed within 3 min of drug administration following either dose of sufentanil. Maximum mean suppression occurred much faster (greater suppression in shorter period of time) with 5.0  $\mu$ g (20% of control at 15 min) than with 2.5  $\mu$ g (60% of control at 30 min). The difference in degree of suppression produced by the two doses at 30 min was statistically significant.

Following the 2.5  $\mu$ g dose, spontaneous and evoked activity were traced as long as possible to evaluate the duration of action. Activity was recorded for 90 min ( $n = 5$ ) and 130 min ( $n = 2$ ). The mean noxiously evoked activity of the two neurons studied for 130 min showed no spontaneous recovery from the level of suppression seen at 30 min (57%) of control. However, the spontaneous activity began to recover from sufentanil suppression at approximately 60 min.

Intravenous naloxone (0.12 mg) was tested on three neurons for each dose of sufentanil. Mean reversal, as shown in figure 3, was only to 89 and 44% of control following 2.5 and 5  $\mu$ g, respectively. Naloxone reversal had begun within 3 min and appeared to reach a maximum within 9 min.

#### INTRAVENOUS ADMINISTRATION

Noxiously evoked activity of the four WDR neurons studied following iv sufentanil was suppressed significantly.

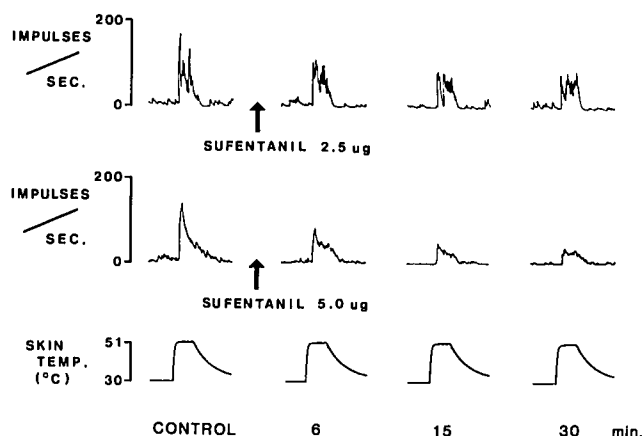


FIG. 2. The effects of sufentanil on two separate WDR neurons are shown. The bottom traces are a record of the skin temperature at the center of the cell's receptive fields. The top two traces depict the effect of 2.5 and 5  $\mu$ g of sufentanil. The left tracing in each represents the control activity evoked by the 51° C, 8-sec radiant heat stimulus. At the arrows, either 2.5 or 5.0  $\mu$ g of sufentanil was placed on the spinal cord. The remaining traces demonstrate the evoked activity at 6, 15, and 30 min after drug administration. At 30 min, the 2.5- $\mu$ g dose had reduced activity to 62% of control, while the 5.0  $\mu$ g dose had reduced the activity to 28% of control.

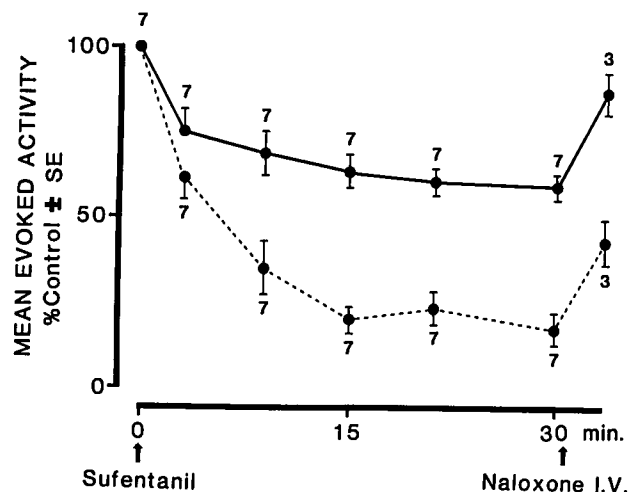


FIG. 3. Effects of 2.5 (solid line) and 5.0  $\mu$ g (dashed line) of sufentanil on the mean noxiously evoked activity of all the neurons studied are shown. The x-axis represents time in minutes after drug injection. The y-axis represents mean noxiously evoked activity expressed as a per cent of control  $\pm$  SE. The numbers above and below the data points indicate the number of cells averaged at each point. The bars indicate  $\pm$  1 SEM. At the 30-min time point, naloxone, 0.12 mg, was administered intravenously in three animals following each dose of sufentanil. The final data point represents activity 3 min after the iv naloxone. The difference between the degree of suppression at 30 min was statistically significant. Note the incomplete reversal of the effects of the 5.0  $\mu$ g dose following iv naloxone.

cantly. Figure 4 shows the time course of suppression of the mean evoked activity. Maximum suppression was seen at the first time point after drug administration. Three minutes after 5  $\mu$ g/kg of iv sufentanil, the activity had been reduced to 40% of control. Following this, spontaneous recovery from sufentanil suppression occurred rapidly and was complete for three of the neurons by the 60-min time point. (It was not possible to maintain adequate recording from the fourth neuron during the last 30 min.)

#### Discussion

The excitement generated by the report by Wang *et al.*<sup>9</sup> that spinally administered morphine could produce intense, long-lasting analgesia without apparent associated block of other sensory modalities, autonomic or motor function has been replaced by the realization that significant problems are associated with the technique. The contribution made by Wang and his co-workers goes far beyond the obvious demonstration of a new analgesic technique. Their findings opened our eyes to the fact that understanding and manipulation of spinal cord pharmacology may provide important clinical tools. With an in-

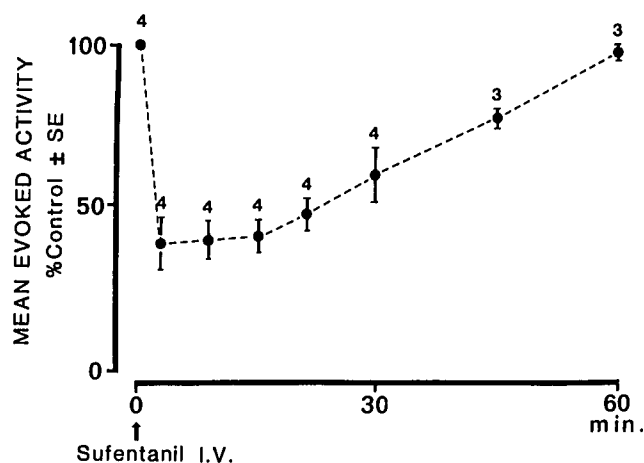


FIG. 4. Effect of 5.0  $\mu\text{g/kg}$  iv sufentanil on mean noxiously evoked activity. See figure 3 for details. Note the very rapid onset and obvious recovery. Contrast this with the time course shown in figure 3.

creased awareness of the spinal cord as a place to do more than administer a local anesthetic, we now need to look for drugs that will be more appropriate for spinal or epidural application. This study reflects such an effort. Sufentanil has a lipid solubility comparable to that of fentanyl;<sup>6</sup> therefore, it should be taken up from the CSF more rapidly than morphine, thus reducing the likelihood of late-onset respiratory depression. The fact that sufentanil dissociates from opiate receptors more slowly than fentanyl<sup>6</sup> may play a role in increasing its duration of action over that of fentanyl. Sufentanil's potency in tail-withdrawal tests in rats is 20 times that of fentanyl,<sup>10</sup> but it has been reported to have a large safety margin in rats and mice.<sup>11</sup> That combination of characteristics may make sufentanil a more appropriate drug than fentanyl for the production of spinal or epidural analgesia.

In light of the many behavioral studies that have demonstrated the ability of fentanyl and its analogues to produce analgesia following spinal or epidural administration, the results of this study (indicating that sufentanil is capable of blocking pain transmission at the level of the spinal cord) are not surprising. There are, however, two findings reported in this study that may be of significance if they are found to occur in humans. The first of these is the duration of the sufentanil effect. Using the same animal model, we previously reported<sup>8</sup> that recovery of evoked activity from 25  $\mu\text{g}$  of spinally administered fentanyl had occurred within 2 h. In this study, no recovery was seen for up to 2 h after 2.5  $\mu\text{g}$  of sufentanil. This is a significant point because the degree of maximum neuronal suppression produced by the 2.5- $\mu\text{g}$  dose of sufentanil was not as great (40% of control) as that produced by the 25- $\mu\text{g}$  dose of fentanyl (11% of control). If we

assume that the maximum suppression of the evoked activity reflects the relative potency of each dose of drug, then the 25- $\mu\text{g}$  dose of fentanyl was more "potent" than the 2.5- $\mu\text{g}$  dose of sufentanil. (Potency as used here does not reflect the precise pharmacological meaning of the word.) Although suppression produced by the fentanyl was greater, recovery was seen within 2 h. In contrast, the 2.5- $\mu\text{g}$  dose of sufentanil produces less suppression, but no recovery of evoked activity was seen within 2 h. These findings, although based on a small number of neurons, suggest that sufentanil spinal analgesia may be of longer duration than that produced by fentanyl.

The second significant finding of this study is the apparent smaller degree of naloxone reversal. We must again point out that our comparison is based on similar endpoints (maximum suppression of noxiously evoked WDR neuron activity), and not on effects produced by drug doses of known equipotency. In previous studies in this laboratory, a 0.1-mg dose of iv naloxone has been shown capable of producing almost complete reversal of suppression of WDR neurons by spinal morphine,<sup>12</sup> fentanyl,<sup>8</sup> and alfentanil (unpublished observations). In contrast, in this study, the naloxone reversal was not as complete. This was in spite of the fact that the spinal sufentanil did not maximally suppress the evoked activity. Several other drugs, including fentanyl, have produced greater degrees of neuronal suppression (to 11% of control). This is an important point because, if maximum suppression had been produced, then it could have been argued that supramaximal concentrations of sufentanil were near the receptors, making it much more difficult for naloxone to reverse the effect. In the fentanyl study, naloxone, 0.1 mg iv, completely reversed the maximum suppression produced by 15  $\mu\text{g}$  (22% of control), as well as that produced by the 25- $\mu\text{g}$  dose (11% of control). We interpret the inability of a slightly higher dose of naloxone, 0.12 mg, to completely reverse the maximum suppression in this study (20% of control) to indicate that more naloxone will be required to reverse sufentanil than is required for the reversal of effects produced by morphine, fentanyl, or alfentanil. This difference may be due to sufentanil's greater affinity for opiate receptors.

The difference in onset and duration seen following spinal *versus* iv drug administration points out the need for careful kinetic studies following spinal administration. Again, we are not comparing equal doses, rather comparable endpoints. The intravenous dose used in this study produced a maximal suppression at 3 min that was midway between that produced by the two spinal doses, but the time course following the two routes is very different. The rate of onset and duration of depression following iv administration clearly would not accurately predict the onset or duration following spinal administration.

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