Dose-response Suppression of Noxiously Evoked Activity of WDR Neurons by Spinally Administered Fentanyl

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The present study examined the influence of spinally administered fentanyl on the spontaneous and noxiously evoked activity of wide dynamic range (WDR) neurons in the dorsal horn of decerebrate, spinal cord-transected cats. This work was performed in order to evaluate the dose-response relationship, time course, and naloxone reversibility of fentanyl suppression of neurons that are involved with the transmission of information about pain. Extracellular single neuron recordings were obtained from 18 WDR neurons in the lumbar enlargement. These neurons were activated by a radiant heat stimulus on the footpads of the hindpaw. Fentanyl (10, 15, 25 µg in 0.5 mL of physiologic saline) was placed on the spinal cord following control studies of each neuron and the effect was observed. In 12 cats, 31 minutes after fentanyl administration, naloxone (0.1 mg) was administered intravenously, and its effect on the fentanyl suppression was determined. All three doses of fentanyl suppressed both the spontaneous and evoked activity of all the neurons studied. Thirty minutes after fentanyl the mean evoked activity was reduced to 47, 23, and 11% of control values by 10, 15, and 25 µg, respectively. The spontaneous activity was reduced to similar levels. Intravenous naloxone (0.1 mg) caused a significant reversal of the fentanyl suppression.

The results of the present study indicate that fentanyl causes a naloxone-reversible, dose-dependent suppression of noxiously evoked WDR neuron activity. Such results support the concept that fentanyl is acting through a specific drug-receptor interaction. The onset of neuronal suppression occurred more rapidly, and the duration of the suppression was longer following fentanyl than that seen following spinal morphine. The onset and duration of this suppression correlates well with human clinical data, providing further evidence that alterations of WDR neuronal activity may be important in the production of spinal opioid analgesia. (Key words: Analgesia. Anesthetic techniques: spinal narcotic. Pain: noxious heat. Spinal cord: WDR neurons.)

RECENT INTEREST in the spinal application of opioids for pain relief has centered attention on the potential importance of spinal pharmacology as it relates to the blocking of afferent pain information. We recently reported effects of spinally administered morphine on noxiously evoked activity of wide dynamic range neurons in the dorsal horn of the spinal cord. However, morphine is a drug of low lipid solubility, and it is felt that opioids of greater lipid solubility may assume an important role in spinal opioid analgesia. It has been suggested that more lipid-soluble opioids may be less likely to produce respiratory depression, which has been seen following spinal or epidural morphine administration. The present study was designed in order to examine the spinal effects of the lipid-soluble opioid, fentanyl, on noxiously evoked activity of neurons in the dorsal horn of the spinal cord. We were particularly interested in determining dose-response relationships, time of onset, and duration of drug effects, as well as the potential naloxone reversibility of any observed effects on the activity of these neurons. Such information, when compared with the previous morphine study and with clinical results, will provide a better understanding of the mechanisms of action and assist in better appreciating the overall efficacy of fentanyl use for spinal opioid analgesia.

Methods

Eighteen cats of either sex (weight 2.7-4 kg) were used (only one neuron was studied in each animal). Neuronal activity was recorded extracellularly from single wide dynamic range (WDR) neurons (WDR neurons are considered to be important for the signaling of the occurrence of noxious peripheral stimulation) as described previously. Both spontaneous and noxiously evoked neuronal activities were recorded during a drug-free control period.

After control studies, saline, which had been bathing the spinal cord, was carefully removed, and the fentanyl-saline solution was applied gently onto the spinal cord. Three doses of fentanyl (10 µg, 15 µg, and 25 µg, six cats each) were studied. Normal saline was used to adjust the volume of fentanyl to 0.5 mL. The solution that was placed on the spinal cord contained no preservatives.

After the application of fentanyl, spontaneous and evoked activity of most cells were measured every 3 min for 30 min. At 31 min, 0.1 mg naloxone was given intravenously to 12 cats. In one cat, naloxone was given spinaly. Neuronal activity in the remaining animals was followed for as long as possible in order to study spontaneous recovery from the effects of fentanyl.

All data were collected on-line and analyzed off-line by a PDP 11/40 computer. In addition, polygraph recordings were made of the skin temperature and the
integrated neuronal activity. The evoked discharge frequency of each neuron was determined by averaging the discharge frequency observed during the time that the radiant heat stimulus caused the firing rate to rise above the spontaneous rate. Spontaneous activity was averaged for 30 s prior to stimulus presentation. Student's paired and unpaired t tests were used for statistical analysis. Differences were considered to be significant if P values were less than 0.05.

Results

All cells studied were individual WDR neurons. All three doses (10 μg, 15 μg, and 25 μg) of spinal fentanyl suppressed both spontaneous and evoked activity of the WDR neurons studied and intravenous naloxone reversed this suppression.

Figure 1 contains plots that indicate the effect of the three doses of fentanyl on the mean evoked activity of all the neurons studied and the subsequent naloxone reversal of those effects. The 25-μg dose produced significantly greater suppression of activity at all time points when compared with the 10-μg dose. The 10-μg dose produced a significant reduction in the mean evoked activity within 6 min of spinal fentanyl administration. Both the 15- and 25-μg doses significantly reduced the mean evoked activity within 3 min of drug administration to 51% and 35% of control, respectively. Following all three doses of fentanyl, 0.1 mg of intravenously administered naloxone caused a significant reversal of the fentanyl suppression. This reversal occurred quickly.

The effects of the three doses of spinally administered fentanyl on the mean spontaneous activity of all the neurons studied are shown in figure 2. All doses produced significant suppression of the mean spontaneous activity within 9 min of the spinal administration of fentanyl. As indicated by the large standard error bars, the effect on spontaneous activity was more variable than that seen on the noxiously evoked activity. Naloxone, 0.1 mg, iv, produced significant reversal of the fentanyl suppression of spontaneous activity within 2 min after administration. The large standard errors are due to the fact that naloxone caused some cells to reach firing rates above those recorded during the control study.

Naloxone, 0.2 mg, was given spinaly in one animal at 33 min after 25 μg spinal fentanyl. The time course after spinal naloxone showed slower onset and slower recovery than that following intravenous naloxone. Onset of recovery began 9 min after spinal naloxone, and another 12 min were required to recover from 14% of control to 68% of control.

The spontaneous recovery of some neurons in the absence of naloxone was studied for various time inter-

vals. None of these neurons (n = 5) showed any indication of recovery for periods of up to 45 min after spinal fentanyl administration. In the one cell from which activity was recorded until recovery was complete, it was found that the evoked activity had returned.
to control values within two hours of fentanyl administration.

**Discussion**

The literature at the present time concerning spinal opioid analgesia contains numerous reports dealing with different drugs which have been administered in an attempt to alleviate many pain states. The drugs have been administered at various concentrations based upon estimates made by the individual researchers. These drugs and their effects have been associated with particular times of onset and duration, many of which are predictable based upon the known pharmacokinetics of the individual agents. There have been, however, incompletely understood effects and side effects resulting from the different pharmacokinetics of these drugs and the different pharmacodynamics of their interaction at the level of the spinal cord. Clinical results reporting spinal fentanyl effects\(^3\)\(^-\)\(^7\) have been excellent except for a few patients, especially during the second stage of labor.\(^8\) Spinal fentanyl appears to be useful for the control of various types of pain.

This present study was carried out in order to determine precise effects of spinally administered fentanyl on a particular population of neurons in the dorsal horn of the spinal cord. WDR neurons are considered to be important for the central relaying of information about pain. They have been identified as being cells of origin of the spinothalamic tract and cells with similar response profiles have been identified in the thalamus and cortex. These neurons, while they do respond to other types of stimuli, respond maximally to stimuli within the noxious range. Thus, the present study enabled us to evaluate the influence of fentanyl upon noxiously evoked activity of neurons that are believed to be involved with the transmission of information about pain. Although species differences do not allow a direct comparison between human and cat data, there is close correspondence between the time course and duration seen in the present study and clinical reports of epidural fentanyl administration. Such a correspondence indicates that studies of the type reported here provide essential information for the elucidation of spinal drug effects.

Clinical reports have indicated that the onset of analgesia following epidural fentanyl administration is approximately 4–10 min.\(^3\)\(^,\)\(^5\) These findings are in keeping with the results found in the present study in which most of the neurons were significantly suppressed within 3 to 6 min after the spinal administration of fentanyl.

Duration of analgesia following epidural fentanyl administration in humans has been reported to be approximately 90–240 min.\(^3\)\^-\(^8\) These results are in keeping with the present study in which the one cell that was followed until recovery returned to its pre-drug control value within approximately two hours.

The present study has demonstrated that there is a dose-response relationship associated with the suppression of noxiously evoked activity of WDR neurons by the spinal administration of fentanyl. Such a relationship supports a specific drug-receptor interaction and also indicates that it should be possible in humans to determine appropriate doses for the alleviation of pain states.

A comparison of the onset of fentanyl suppression with that seen following spinal morphine reveals that fentanyl is capable of producing a much more rapid
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depression of noxiously evoked activity than is mor-
phine. For instance, 15 μg of fentanyl produced near
maximal suppression within six minutes after its admin-
istration, while the same level of suppression produced
by 0.25 mg of morphine was not apparent until ap-
proximately 24 min after its administration. The rapid
effect of fentanyl is likely to be due to greater lipid
solubility allowing the drug to penetrate to sites of ac-
tion much more rapidly. If that is the case, then it is
likely that such a rapid uptake will result in lower CSF
levels of the drug and thus reduce the amount of drug
available for cephalad transport in the CSF. Such a re-
duction is likely to decrease the chance of respiratory
depression.2

An important finding of the present study is the nal-
oxone reversibility of the suppression of noxiously
evoked activity by the spinally administered fentanyl.
In several neurons that were studied for times greater
than 30 min without the administration of naloxone,
there was no obvious spontaneous recovery from the
drug up to at least 45 min. This would indicate that in
those neurons in which naloxone caused a reversal of
the effect, that reversal was indeed a drug effect and
not simply a result of recovery from fentanyl adminis-
tration. The presence of this naloxone reversal indicates
that the suppression of noxiously evoked activity of
WDR neurons by the spinal administration of fentanyl
is caused by an interaction of fentanyl with specific opi-
ate receptors rather than by a nonspecific overall
suppression of neuronal activity (e.g., local anesthetic
effect). This is further evidence for a specific drug-re-
ceptor interaction.

In summary, the results of the present study indicate
that the spinal administration of fentanyl is capable of
suppressing noxiously evoked activity of WDR neurons
in the dorsal horn of the spinal cord in a dose-related
manner and that the intravenous administration of nal-
oxone will reverse that suppression. The close corre-
lation between the time course of fentanyl effects in
humans and in this study indicates that suppression of
WDR neurons may be important to the production of
analgesia. This effect appears to be mediated by a spe-
cific drug-opiate receptor interaction.

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