

Title: SPINAL OPIATE ANALGESIA WITH FENTANYL, ITS MECHANISM AND NALOXONE REVERSAL

Authors: M. Suzukawa, M.D., M. Matsumoto, M.D., J.G. Collins, Ph.D., and L.M. Kitahata, M.D., Ph.D.

Affiliation: Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut 06510

**Introduction.** The potential importance of spinal opioid administration demands careful study of its underlying mechanisms. We therefore designed the present study to examine the influence of fentanyl on dorsal horn neurons which respond to noxious peripheral stimulation. Our goal was to determine the dose-response relationships, time of onset and naloxone reversibility of the fentanyl effects on individual neurons and to compare these results with clinical findings.

**Methods.** Cats of either sex, ranging in weight from 2.5 to 4.5 kg, were prepared for extracellular single neuron recording from wide dynamic range neurons in the dorsal horn of the spinal cord. Initial surgical preparation was made under halothane- $O_2$ - $N_2O$  anesthesia which was discontinued following spinal cord transection at T-12 and decerebration by electrolytic midbrain reticular formation lesions. Physiologic parameters were monitored and maintained within normal limits. A laminectomy was performed at L-4 through L-6, the dura was incised and the spinal cord covered with normal saline. Tungsten microelectrodes were used to record neuronal activity. After physiologic identification of a single WDR neuron, a  $51^{\circ}C$  radiant heat stimulus (8 second duration) was used as a noxious stimulus to the appropriate receptive field on the foot pad. Following control studies, the normal saline which had been bathing the spinal cord was carefully removed and fentanyl, either 10  $\mu g$  or 25  $\mu g$  (6 cats each, both in 0.5 ml of normal saline) was administered gently onto the spinal cord. Subsequent to drug administration, spontaneous and evoked activity were recorded every 3 minutes up to 30 minutes. At 31 minutes, 4 out of 6 cats for each dose were given 0.1 mg of naloxone intravenously, and all activity was again observed every 3 minutes.

**Results.** Intrathecally applied fentanyl suppressed both the spontaneous and evoked activity of all the WDR neurons studied. The effects of 10 and 25  $\mu g$  of spinally administered fentanyl on the mean evoked activity are shown in Figure 1. The 10  $\mu g$  dose produced significant suppression ( $p < 0.05$ ) within 6 minutes. The 25  $\mu g$  dose produced significant suppression within 3 minutes. The suppression produced by the 25  $\mu g$  dose was significantly greater than the 10  $\mu g$  dose at all time points. Within two minutes, 0.1 mg of intravenously administered naloxone signi-

ficantly reversed the suppression produced by both doses of spinally administered fentanyl.

**Discussion.** This, to the authors' knowledge, is the first report of the suppression of noxiously activated spinal neurons by spinally administered fentanyl. The suppression occurred in a dose related manner, had an onset that was comparable to that seen clinically<sup>1</sup> and was reversed by naloxone. The presence of a dose response relationship in experimental animals suggests that an optimal dosage can be determined for the production of analgesia in humans. The short time course is in contrast to the longer onset seen clinically and in animal experiments following spinal morphine administration.<sup>2</sup> The similarity between the clinical time course and that observed in the present study suggests that suppression of WDR neurons is important to the production of spinal opioid analgesia. The naloxone reversal provides further evidence that opiate receptors are intimately involved in the production of spinal opioid analgesia.

(Supported by NIH Grant NS-09871)

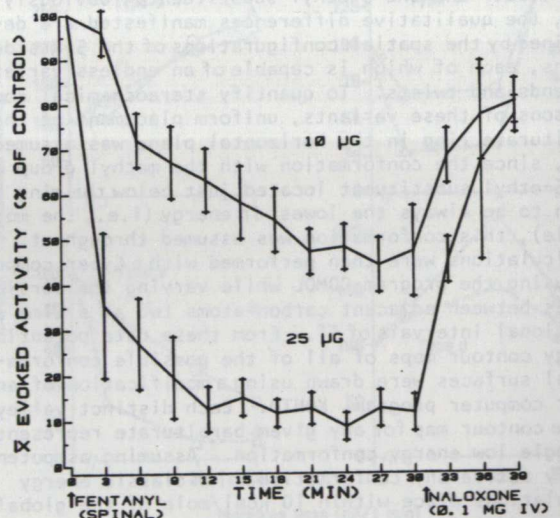


Fig. 1. Fentanyl suppression of mean noxiously evoked activity and subsequent naloxone reversal of that suppression.

**References.**

1. Wolfe MJ, Nicholas ADG: Selective epidural analgesia. *The Lancet* 1:150, 1979.
2. Homma E, Collins JG, Kitahata LM et al: Suppression of noxiously evoked WDR dorsal horn neuronal activity by spinally administered morphine (Submitted).