Quantitation and Selective Blockade of Response to Narcotic Analgesics in the Horse

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During the course of some pharmacokinetic experiments with fentanyl,[3] we observed marked signs of locomotor stimulation in horses. Because most racing commissions consider fentanyl a depressant drug, we elected to define and characterize this stimulant action of fentanyl. To this end, we developed a simple "step counting" procedure in which the number of steps that a horse takes with its left foreleg in each two minute period following the injection of a drug is tallied and plotted.[4] This method allowed remarkable accurate and reproducible quantitation of the locomotor stimulant actions of fentanyl and was also applicable to other narcotic analgesic drugs in the horse.[1]

The locomotor response to increasing doses of fentanyl in four horses is presented in Fig. 1. The straight line at the bottom of the graph represents the locomotor response to saline injection, while the other curves represent the response to increasing doses of fentanyl. When given intravenously (IV), fentanyl rapidly increased spontaneous motor activity, up to 25 times baseline activity. This effect peaked at about four minutes after dosing and then declined exponentially to control levels. Other experiments have shown this effect to be remarkably consistent and reproducible (Fig. 4). The locomotor response to IV fentanyl may, therefore, become a useful probe for studying the effects of drugs on behavior in the horse.

The effects of morphine on spontaneous motor activity in the horse are shown in Fig. 2. With morphine, much larger doses on a mg/kg basis were required to produce the same peak locomotor response, but the response was correspondingly prolonged. Thus, at 2.4 mg/kg of morphine IV, the motor effect peaked at about 90 steps/2 minutes, three hours after dosing and took 14 hours to return to control. This was the longest period of action for any of the narcotic analgesics tested in these experiments.

A family of dose response curves representing peak response/dose for a number of narcotic analgesics is shown in Fig. 3. Fentanyl was clearly the most potent narcotic analgesic tested, followed by hydromorphone, methadone, anileridine, morphine, pentazocine and meperidine. This is the same rank order of potency as is observed for the analgesic action of these drugs in the human. Other parallels exist between the action of fentanyl and pentazocine in the human and the horse which suggest that this locomotor response closely parallels the analgesic efficacy of these drugs in the horse.[5]

Selective blockade of the locomotor response to these drugs is shown in Fig. 4. In this experiment, horses were pretreated with naloxone or acepromazine and then challenged with fentanyl IV. Pretreatment with naloxone completely blocked the response to fentanyl. On the other hand,

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pretreatment with acepromazine only partially blocked the fentanyl response and this blockade took almost two hours to peak after IV administration of acepromazine. By six hours postdosing, the phenothiazine blockade had disappeared. The naloxone block shows that the locomotor response to fentanyl requires occupation of opiate receptors and the acepromazine block suggests that the effect is also dependent on activation of dopaminergic systems in the CNS.

Summary

1. All seven narcotic analgesics tested produced locomotor stimulation in the horse.
2. A simple step counting method for quantitating this effect was presented.
3. The rank order in which these drugs produced their locomotor response is the same as their analgesic potency in man.
4. The time course of the locomotor response to narcotic analgesics in horses differs markedly from the time course of the analgesic effect in man for some narcotics.
5. The locomotor response was blocked by either naloxone or acepromazine.
6. It may be possible to develop a narcotic-phenothiazine cocktail which will reduce the motor response to narcotics in the horse, but retain their useful analgesic actions.

References

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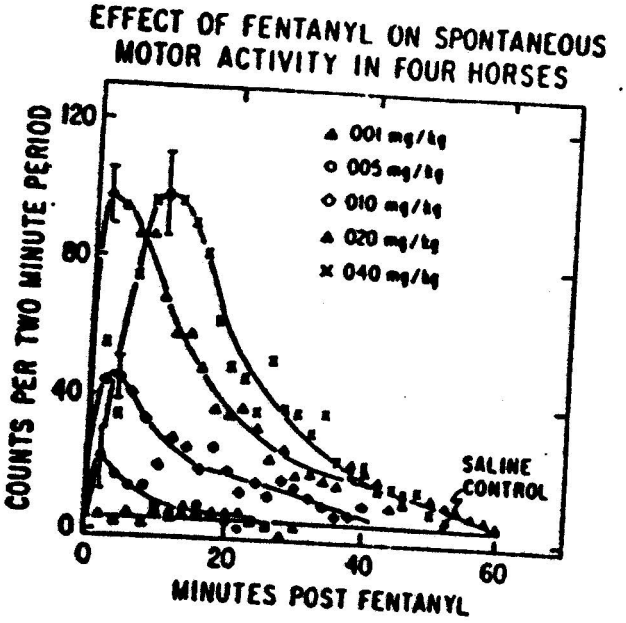


Fig. 1. Effect of fentanyl on locomotor activity in four horses.

Horses were injected with saline or increasing doses of fentanyl IV. The average counts per 2-minute period following saline injection are shown by the straight line near the bottom of the graph. The response to .001 mg/kg fentanyl is shown by the open triangles (Δ - Δ); .005 mg/kg fentanyl, open circles (○- ○); .010 mg/kg fentanyl, open diamonds (◇-◇); 0.30 mg/kg solid triangles (▲- ▲); and .040 mg/kg fentanyl by crosses (× - ×). At the highest dose tested all horses showed a loss of coordination resulting in a decrease in locomotion during the first 6 minutes. All points are the means of counts determined on 4 horses and the vertical bars represent S.E.M.'s.

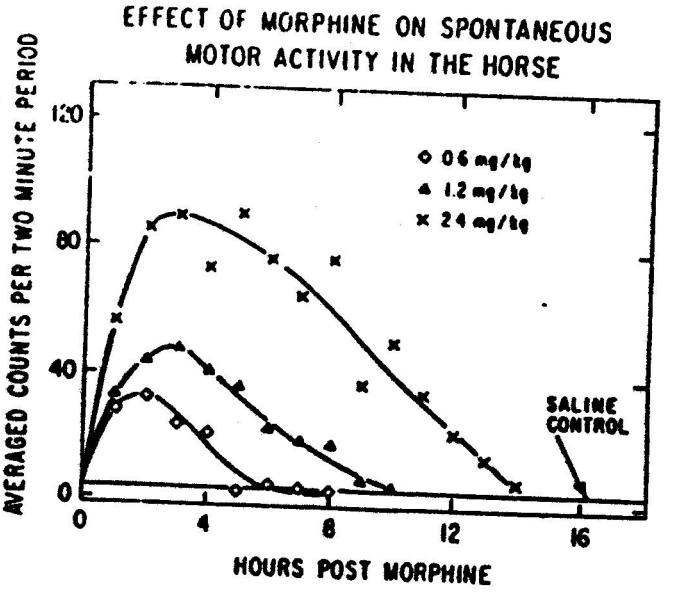


Fig. 2. Effect of morphine on spontaneous motor activity in the horse.

Horses were injected IV with saline and increasing doses of morphine. The average counts per 2-min period following saline injection are shown by the straight line near the bottom of the graph. The response to 0.6 mg/kg morphine is shown by the open diamonds (◇ - ◇); 1.2 mg/kg morphine by the closed triangles (▲ - ▲), and 2.4 mg/kg morphine by the crosses (X - X). Averaged counts per 2 min period were determined for the 16-min interval immediately preceding the time indicated. All points are the means of such averaged counts on 4 horses.

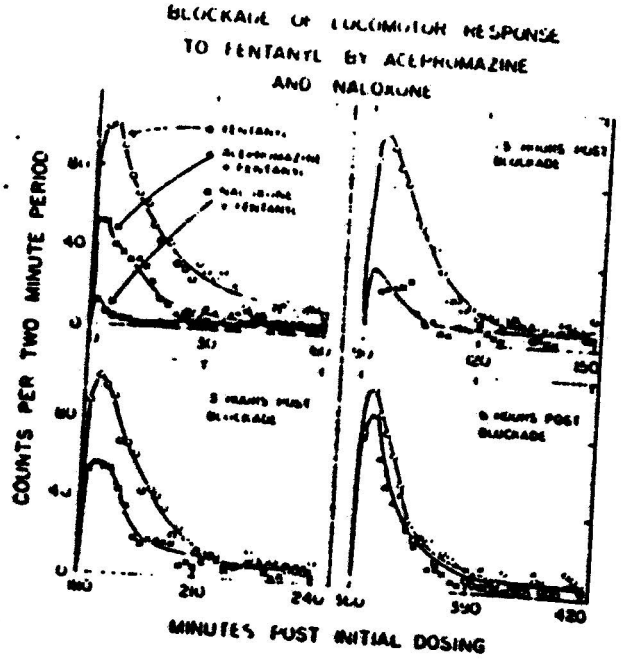
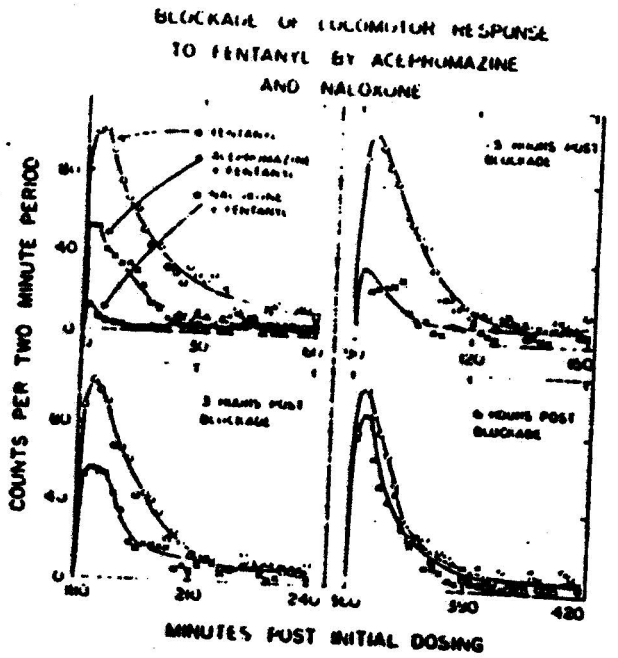


Fig. 4. Blockade of the Locomotor Response to Fentanyl by Acepromazine and Naloxone.

Horses were pretreated with acepromazine (0.1 mg/kg) or naloxone (0.015 mg/kg) intravenously at 15 and 5 mins, respectively, before challenge with fentanyl, 0.02 mg/kg. The open circles (○ - ○) show the locomotor response of non-pretreated horses challenged with fentanyl at 0, 1.5, 3.0 and 6 hrs. The solid squares (■ - ■) show the response to fentanyl after pre-treatment with naloxone, while the crosses (X - X) show the response after pre-treatment with acepromazine. All experimental points are the means of experiments on three horses.



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