

# Pharmacology of Narcotic Analgesics in the Horse: Selective Blockade of Narcotic-Induced Locomotor Activity

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## SUMMARY

The locomotor responses of horses given morphine and fentanyl were blocked or lessened by administration of naloxone or acepromazine. Naloxone given at the dosage of 0.015 mg/kg completely blocked the locomotor activity induced in horses given fentanyl (0.020 mg/kg of body weight).

The locomotor stimulation produced by morphine given at the dosage of 2.4 mg/kg was reduced by 75% by naloxone (0.020 mg/kg).

Acepromazine partially blocked the locomotor responses to fentanyl and morphine. This blockade activity reached its peak about 30 minutes after acepromazine was given (iv) and lasted more than 6 hours. Simultaneous administration of acepromazine and morphine was associated with substantial respiratory depression for more than 4 hours after administration of both drugs.

In other experiments, fentanyl did not add to the partial locomotor response observed after large doses of pentazocine were given—this being consistent with the concept that pentazocine possesses both antagonist and agonist actions at the narcotic receptor. Furosemide and phenylbutazone, given at usually used clinical doses, had no effect on the locomotor response to fentanyl, indicating that the usual clinical dosages of neither drug exerted stimulant or depressant actions.

sponds closely with the time course of the locomotor stimulation in horses.<sup>4</sup> Pentazocine, which appears to be only a partial agonist of analgesic receptors in persons and horses, similarly produces partial and short-lived analgesic and locomotor responses in the horse.<sup>1</sup> These relationships indicate that the locomotor response to narcotic analgesics in the horse may be dependent on occupation of opiate receptors by these drugs, similar to those receptors at which these drugs produce analgesia.

There is substantial evidence implicating the role of the dopaminergic pathways in locomotor responses to drugs.<sup>7</sup> Since apomorphine, a dopamine agonist,<sup>7</sup> produces a response in the horse resembling that of the narcotic analgesics,<sup>4,8</sup> it appears likely that a dopaminergic pathway is involved in the locomotor response to narcotic analgesics. Because of these considerations, we studied the effects of a narcotic antagonist and a phenothiazine tranquilizer on the locomotor response to narcotic analgesics. The data indicate that this response is very sensitive to inhibition by both of these drugs, supporting suggestions that both opiate and dopaminergic receptors are involved in the locomotor response of horses to narcotic analgesics.

## Materials and Methods

Mature Thoroughbred or Standardbred horses, between 4 and 18 years of age and 400 and 550 kg (body weight), were used. The animals were kept at pasture and brought into the specially shielded box stalls at least 24 hours before an experiment was begun. The box stalls measured 16 m<sup>2</sup>, had straw-covered earthen floors, and plywood sheeting on the box grillwork to reduce interaction with horses in other stalls. A small glass window (0.3 × 0.3 m) in the plywood shielding was used for observation. Before the start of an experiment, feed and water buckets were removed from the stall.

During the experimental period, the horse was scored for 1 event if he lifted his left foreleg and took a step. Movements of the left leg not resulting in relocation of the foot, such as scratching or pawing, were not counted. To assist the observer in scoring these events, the left leg of the horse was wrapped in white tape. Each event was tallied on a hand counter<sup>a</sup> and the cumulative score was logged for 2-minute periods.<sup>b</sup>

The reliability and reproducibility of the observational measurement technique were verified by the use of 2 independent observers in 1 of the experiments concerning fentanyl.<sup>5</sup> Percentage of agreement between 2 observers was determined for each 2-minute period by dividing the smaller of the event totals by the larger event total. These percentages were averaged across 35 two-minute periods and gave an overall percentage of agreement of 96.17%. The appropriateness of this procedure was verified by

Reports from our laboratory indicate that narcotic analgesics produce a characteristic dose-dependent increase in "spontaneous" locomotor activity in the horse.<sup>1-6</sup> This response is dose related, and the rank order in which the narcotic analgesics produce this response is the same as the rank order in which they produce analgesia in persons.<sup>1</sup> The time course of fentanyl-induced analgesia in persons corre-

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<sup>a</sup> Veeder-Root Inc, Hartford, Conn.

<sup>b</sup> Electronic Stop Watch, Cronus Precision Products, Santa Clara, Calif.

calculating the correlation between the 2 observers' scores, which yielded a 0.998 correlation coefficient.<sup>5</sup>

All drugs (Table 1) were given by iv injection, except for the furosemide treatments which were administered IM.

Base-line activity for each horse, determined following iv injection of saline solution, amounted to an overall average of 4 steps/2-minute counting period. For experiments with fentanyl,<sup>6</sup> raw counts for a 2-minute period were plotted against time as described previously.<sup>1</sup> For drugs with a longer duration of action (such as morphine<sup>4</sup> and pentazocine<sup>7</sup>), the total number of steps in a 2-minute period was averaged for 16-minute periods and these mean activities were plotted. Sufficient time was allowed between doses to preclude the possibility of sequential or tolerance effects.

## Results

**Experiment 1**—Three horses were given morphine (2.4 mg/kg). Locomotor activity was maximal at about 85 steps/counting period (2 minutes), a 20-fold increase over base-line activity as measured after saline solution injection. At this dose of morphine, the horses were poorly coordinated and appeared unaware of their surroundings, often bumping into walls. This incoordination lasted up to 7 hours,<sup>1</sup> and during the time of highest locomotor activity, the horses would not stop to eat, although they often carried hay in their mouths.

**Experiment 2**—In horses given the same dosage level of morphine, study was made of the effects of treatment with naloxone after the morphine-induced locomotor activity was allowed to develop. In this series, 1 hour after injection of morphine, 3 horses were treated with chemically pure crystalline naloxone HCl<sup>8</sup> (0.020 mg/kg) dissolved in distilled water, and 2 horses were given commercial naloxone<sup>9</sup> (0.020 mg/kg). The results of the blockade by the crystalline naloxone are illustrated in Figure 1. There was no statistical difference (paired data *t* test, *P* < 0.01) between the locomotor responses of the 3 naloxone-treated horses and the 2 animals treated with the commercially available form.

The horses regained coordination and alertness within a minute after the iv administration of the narcotic antagonist, and the morphine-elicited locomotor activity was effectively reduced by an average of 75%. This blockade was most complete immediately after the injection of the antagonist, with a slight increase in locomotor activity peaking at about 8 hours. By this time, morphine-induced locomotor activity would normally begin to lessen, thus accounting for the absence of any further increase of locomotor activity as the naloxone effects diminished.

**Experiment 3**—Figure 2 shows the effects of acepromazine<sup>4</sup> on the locomotor response in 4 horses dosed with morphine (0.6 mg/kg). (This smaller dose of morphine was given because preliminary experiments showed that the blocking effect of acepromazine was relatively short lived.) The data show that acepromazine given at the dosage of 0.16 mg/kg markedly reduced the locomotor response during the 1st hour. Two of the 4 horses spent long periods of quiet standing through the end of the 1st hour. The 3rd horse remained within the range of normal base-line loco-

TABLE 1—Experimental Procedure

Experiment No.	No. of horses	Drugs	Doses (mg/kg)	Schedule
1	3	Morphine sulfate	2.4	—
2	5	Morphine sulfate	2.4	—
		Naloxone HCl, crystalline	0.020	1 Hour after morphine
		Narcan	0.020	1 Hour after morphine
3	4	Morphine sulfate	0.6	Given at same time in separate syringes
		Acepromazine maleate	0.16	
4	4	Fentanyl citrate	0.020	—
		Acepromazine maleate	0.1	15 Minutes before fentanyl
		Narcan	0.15	5 Minutes before fentanyl
5	4	Fentanyl citrate	0.020	—
		Pentazocine HCl	2.0	30 Minutes before fentanyl
6	4	Fentanyl citrate	0.020	—
		Furosemide	1.0	45 Minutes before fentanyl
		Phenylbutazone	6.6	3 Hours before fentanyl

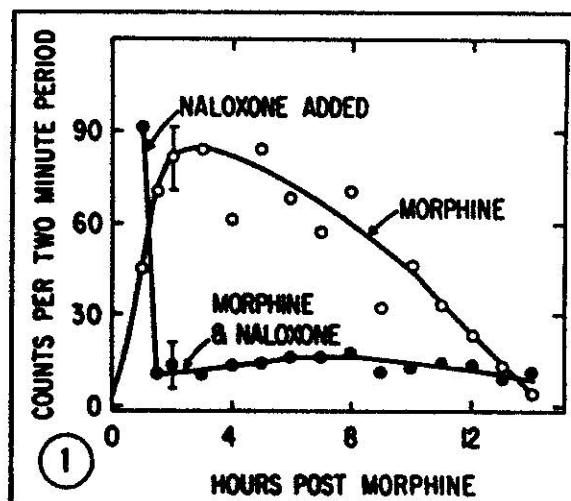


Fig 1—Effects of naloxone on morphine-induced locomotor activity (experiment 2). The open circles (○—○) represent the mean locomotor response of 3 horses given morphine iv at a dosage of 2.4 mg/kg. The solid circles (●—●) represent the mean locomotor response of the same 3 horses dosed with morphine iv at a dosage of 2.4 mg/kg and challenge exposed with naloxone (0.02 mg/kg) at 60 minutes after administration of morphine. Representative standard errors are plotted.

motor activity during the 1st hour, and the 4th horse exhibited a slight increase above that seen during base-line activity, during this initial time span. Thus, the 4 animals exhibited activity well below that which would be expected following dosing with morphine alone. In fact, the morphine and subsequent acepromazine combination resulted in only 48% of the total counts obtained following dosing with morphine alone.

Since morphine and acepromazine are respiratory depressants in the horse,<sup>10,11</sup> the effects of this combination of drugs on respiratory rate were determined. As shown in Figure 3, the respiratory rate of these horses was almost 50% inhibited within 20 minutes of dosing with both drugs and remained depressed for the 4 hours during which respiratory rate was counted; between 6 and 8 hours, respira-

<sup>1</sup> McNeil Laboratories, Fort Washington, Pa.

<sup>2</sup> Eli Lilly & Co, Indianapolis, Ind.

<sup>3</sup> Winthrop Laboratories Inc, New York, NY.

<sup>4</sup> Endo Laboratories Inc, Garden City, NY.

<sup>5</sup> Narcan, Endo Laboratories, Garden City, NY.

<sup>6</sup> Ayerst Laboratories, New York, NY.

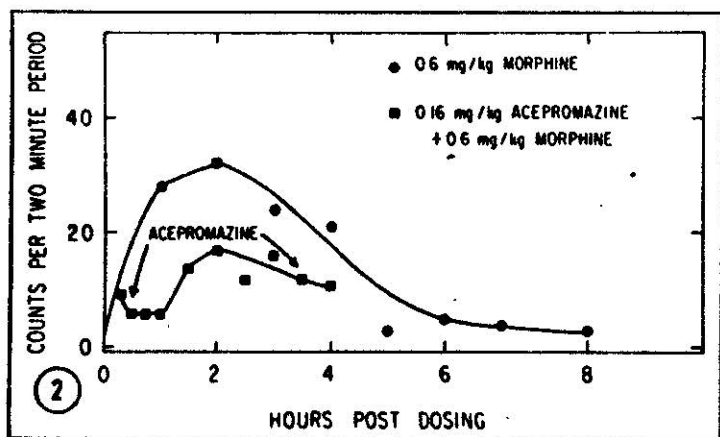


Fig 2—Blockade of locomotor response to morphine by acepromazine (experiment 3). The locomotor response of horses given morphine at a dosage of 0.6 mg/kg is shown by the closed circles (●—●). The response to a combination of acepromazine (0.16 mg/kg) and morphine (0.6 mg/kg) is represented by the solid squares (■—■). All data points represent means of experiments in 4 horses. The average SEM for the first 3 hours for morphine alone was  $\pm 6.0$  and for the morphine-acepromazine combination,  $\pm 6.6$ .

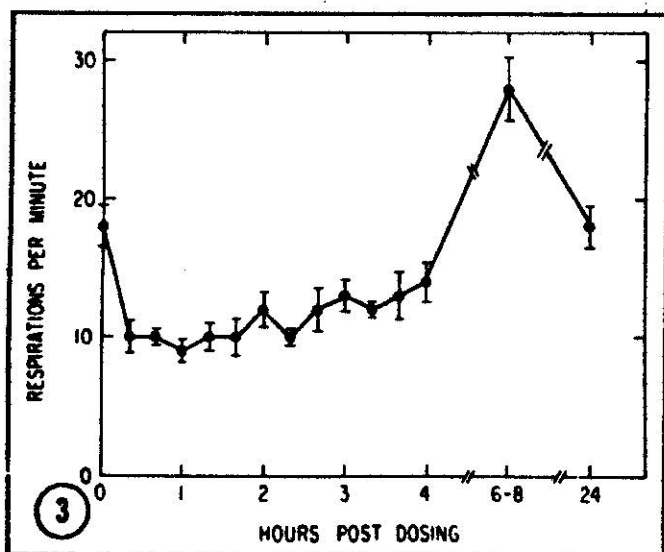


Fig 3—Respiratory rate response to acepromazine and morphine (experiment 3). The solid circles (●—●) show the mean respiratory ( $\pm$  SEM) rate in 4 horses after dosing with morphine (0.6 mg/kg) and acepromazine (0.16 mg/kg).

tory rates were greater than control, and by the next day, the respiratory rates had returned to base line.

**Experiment 4**—While the earlier experiments demonstrated that both naloxone and acepromazine blocked the motor response in horses given morphine, they did not allow making a determination of the time course of these effects. Because the motor response to iv fentanyl is brief, highly reproducible, and likely terminated by redistribution of the drug,<sup>1</sup> we pretreated animals with both acepromazine and naloxone and then gave them (iv) fentanyl 4 times at 90-minute intervals. As shown in Figure 4, the locomotor responses after repeated doses were quite reproducible with mean peak responses for 3 horses ranging between 101 and 103 steps/2-minute counting period, although there was

some decrease in the areas under the curves with repeated dosing. This represented a 25-fold increase over base-line activity. In 1 test series, each of 3 horses was injected with acepromazine (0.1 mg/kg) iv; starting 15 minutes later, 4 doses of fentanyl were given, 90 minutes between doses (at 0, 90, 180, and 360 minutes). The fentanyl response was only partially blocked by the pretreatment with acepromazine, with the greatest depression in activity occurring at 90 minutes, and the blockade was almost gone by 6 hours. The pretreatment of the 3 horses with commercial naloxone (0.015 mg/kg) at 5 minutes before the 1st fentanyl injection almost completely blocked the response to fentanyl. The naloxone blockade wore off slowly, being still very much in evidence at 6 hours.

Because the areas under the fentanyl response curves decreased with repeated dosing, the areas under all curves were determined with a compensating polar planimeter and the inhibited responses were plotted as a percentage of the corresponding control responses (Fig 5). Blockade of the fentanyl response by acepromazine in 3 horses was greatest at 90 minutes, being only 34% of the base-line response, while locomotor activity had returned to 86% of base line by 6 hours. Naloxone pretreatment resulted in essentially complete elimination of the response to fentanyl. Five minutes after naloxone was given, only 7% of the expected locomotor response to fentanyl was obtained and this level of activity was close to that seen following the injection of saline solution. Blockade due to naloxone wore off slowly and only 50% of the normal locomotor response to fentanyl was observed at 6 hours after blockade.

**Experiment 5**—Pentazocine is considered to be a mixed narcotic agonist-antagonist. To determine whether this drug partially or fully occupied the receptor sites at which locomotor activity is stimulated, 4 horses were given a

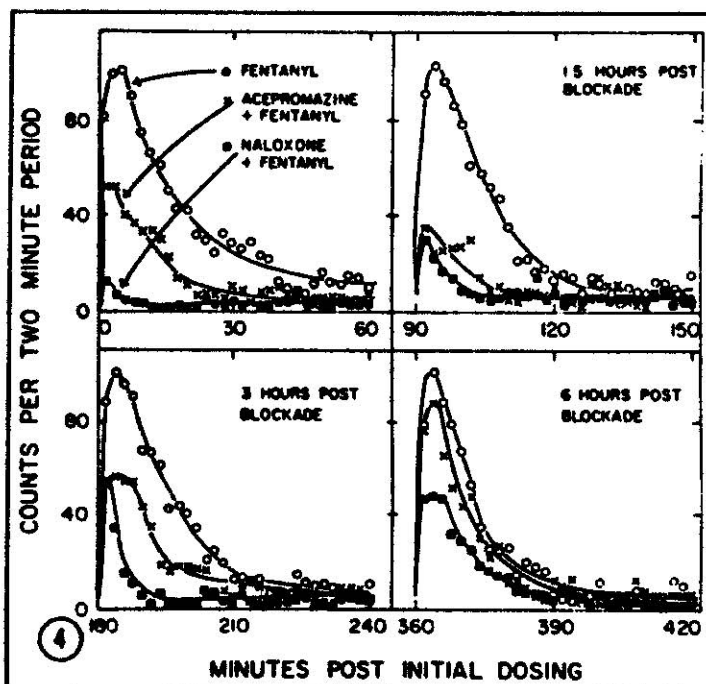


Fig 4—Blockade of the locomotor response to fentanyl by acepromazine and naloxone (experiment 4). Horses were pretreated with either acepromazine (0.1 mg/kg) or naloxone (0.015 mg/kg) at 15 and 5 minutes, respectively, before they were given a series of 4 doses of fentanyl (0.020 mg/kg). The SEM at peak activity for the 1st dose of fentanyl ranged between  $\pm 4.4$  and  $\pm 5.6$  counts.

<sup>1</sup> Comble J, Tobin T: The pharmacology of narcotic analgesics in the horse. VI. The pharmacokinetics, metabolism and detection of fentanyl. Manuscript in preparation, 1980.

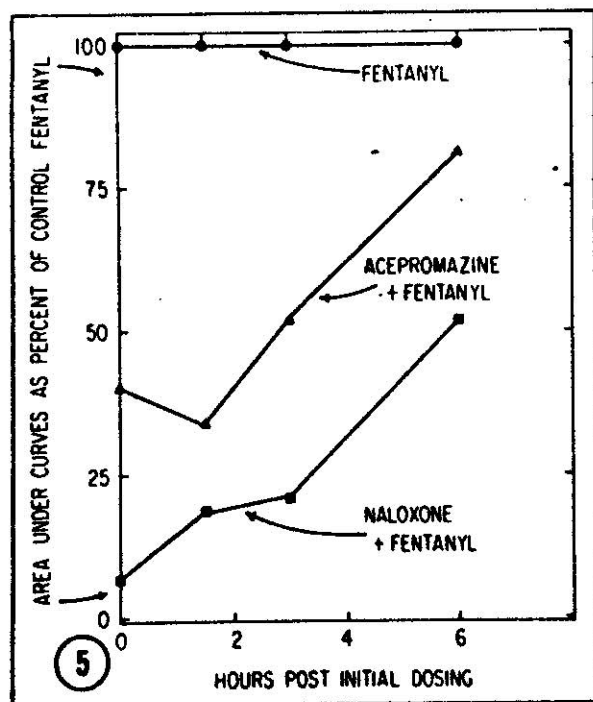


Fig 5—Normalized time course of blockade of fentanyl response by acepromazine and naloxone (experiment 4). The area under each locomotor activity curve in Figure 4 was determined, using a compensating polar planimeter. The solid circles (●—●) represent areas under the activity curves after treatment with fentanyl alone, arbitrarily set as 100% for each dose. The triangles (▲—▲) show the normalized area under the curves from horses given acepromazine and fentanyl, and the solid squares (■—■), from horses dosed with naloxone and fentanyl.

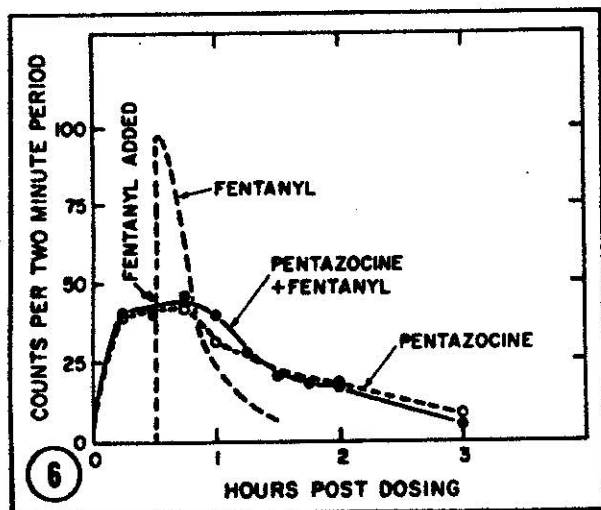


Fig 6—Blockade of locomotor response to fentanyl by pentazocine (experiment 5). The open circles (○—○) show the locomotor response of horses given pentazocine iv (2.0 mg/kg). The solid circles (●—●) show the locomotor response when this dose of pentazocine was followed at 30 minutes by fentanyl iv (0.02 mg/kg). The normal locomotor response to a dose of fentanyl alone is indicated by the dotted line. All data points are the means of experiments on 4 different horses. The SEM for the 1st point on the pentazocine curve was  $\pm 2.6$  and on the pentazocine plus fentanyl curve,  $\pm 6.3$ .

maximum amount of pentazocine followed by a large dose of fentanyl. As shown in Figure 6, fentanyl was ineffective in the presence of pentazocine, indicating occupation by pentazocine of all the receptors at which fentanyl stimulates locomotor activity.

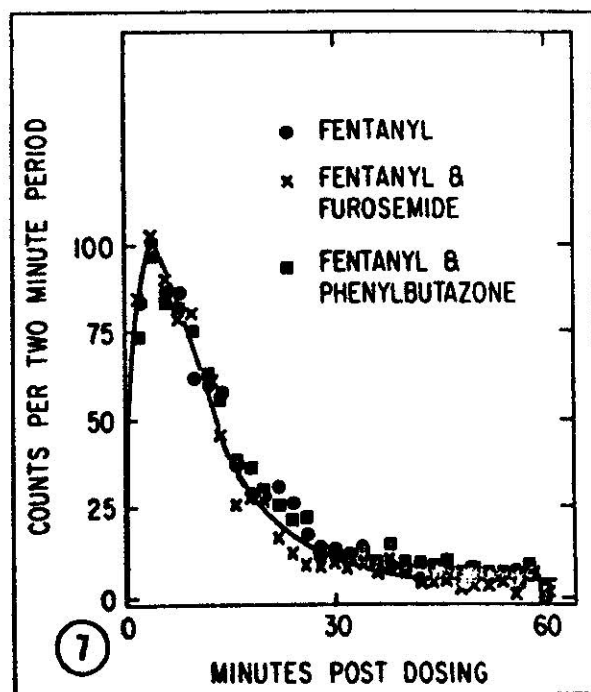


Fig 7—Fentanyl-induced locomotor activity in furosemide and phenylbutazone-pretreated horses (experiment 6). Four horses were dosed in 3 separate experiments as follows: (a) fentanyl (locomotor response shown by the closed circles, ●—●); (b) fentanyl 45 minutes after pretreatment with furosemide iv (locomotor response shown by crosses, X—X); and (c) fentanyl 3 hours after treatment with phenylbutazone iv (locomotor response shown by solid squares, ■—■). A paired data *t* test indicated no significant difference between horses pretreated with furosemide or phenylbutazone and control horses at  $P < 0.01$ .

**Experiment 6**—Since it is impossible to observe a significant decrease in locomotor activity below a base line of only 4 steps/2-minute counting period, drugs possibly acting as depressants were studied by observing their effect on the reproducible and reliable fentanyl response. Figure 7 shows results of this type of experiment done with phenylbutazone<sup>1</sup> and furosemide.<sup>2</sup> A paired data *t* test ( $P < 0.01$ ) determined that there was no significant inhibition of locomotor response in horses pretreated with either phenylbutazone or furosemide, indicating no significant calming or tranquilizing effects of these drugs.

## Discussion

The locomotor response of horses given morphine and fentanyl was sensitive to naloxone and acepromazine. A sufficiently large dose of naloxone rapidly and almost completely blocked the opiate-induced locomotor response. With large doses of fentanyl (0.020 mg/kg), naloxone given in the dosage of 0.015 mg/kg was sufficient to prevent the agonist-induced locomotor stimulation. The blockade was nearly complete at first and wore off slowly, these horses still were 50% protected up to 6 hours later. The large dose of morphine required more naloxone (0.020 mg/kg) to give a 75% reduction in activity, indicating that more naloxone would be required to achieve a completely effective blockade of the locomotor response.

Naloxone, in its chemically pure and commercial forms, is a pure narcotic antagonist with the ability to reverse or

<sup>1</sup> W. A. Butler Co, Columbus, Ohio.

<sup>2</sup> National Laboratories Corp, Somerville, NJ.

terminate many of the effects of the narcotic analgesics in persons, including depression, analgesia, convulsions, coma, psychotogenesis, and dysphoria.<sup>12</sup> In our studies, pretreatment with commercial naloxone almost completely blocked the locomotor response to fentanyl. The blockade slowly wore off, and this is in good agreement with the findings in persons that the half-life of commonly used clinical doses may be only several hours.<sup>12</sup> Other effects we had previously found to be induced by fentanyl, such as increased propensity to eat during low locomotor activity,<sup>1</sup> was not blocked. Indeed, with the decrease in locomotion, an increase in eating behavior was observed.

Commercial naloxone at a dosage of 0.005 mg/kg given twice had relatively little effect on the locomotor activity of a horse treated with a large dose of morphine. Although the locomotor activity did decrease, it quickly returned to roughly 80% of the level of activity expected from horses given morphine alone. Coordination was immediately regained upon administration of naloxone and was not impaired again, even though locomotor activity returned to fairly high levels usually associated with incoordination. However, 0.02 mg of naloxone/kg given iv in 2 ml of distilled water rapidly and completely reversed the locomotor effects of morphine for 13 hours.

Because pentazocine only produced a partial locomotor response in our previous studies,<sup>1</sup> the question arose whether pentazocine produced its effects by occupying only a fraction of the receptors at which the locomotor response was stimulated or all of the receptors in a partially effective fashion. To distinguish between these possibilities, horses were given sufficient pentazocine to produce a maximal pentazocine-induced locomotor response. Then, at peak response we challenge exposed these horses with an additional dose of fentanyl (0.02 mg/kg), sufficient to yield a peak motor response of about 100 steps/2-minute period. However, as shown in Figure 6, this dose of fentanyl produced no significant increase in locomotor activity nor were any other changes in clinical signs or behavior noted. The simplest interpretation of these results is that pentazocine had occupied all the receptors normally available to fentanyl and prevented any pharmacologic effects from the challenging dose of fentanyl.

Acepromazine is one of the most extensively used phenothiazine derivatives in equine practice, but despite this wide use, little useful information has been published about its dose-response relationships or time course of action. Fraser<sup>13</sup> reported that acepromazine administered IM is effective within 2 or 3 minutes and has a duration of action of about 30 minutes, which must be considered an unusually rapid and brief period of action for a drug after IM injection.

Because the central effects of fentanyl in the horse are apparently rapidly terminated by redistribution of this drug, one might reasonably expect to get reproducible responses to this drug with only small intervals between doses. Such a model could then be used to quantitate dose response and time course relationships for drugs such as acepromazine in the horse. As shown in Figure 4, the peak responses to fentanyl were remarkably consistent with 4 consecutive doses, peaking at between 101 and 103 steps/2-minute period in each horse. The areas under the activity curves, however, decreased with each subsequent dose, to 64% of the base line after the 4th dose.

We, therefore, chose to replot the inhibition data as percentage of each individual control value to eliminate base-line drift due to the changing response to fentanyl. As

shown in Figure 5, the greatest response to acepromazine was observed at 105 minutes after dosing, although it appears likely that actual peak response occurred earlier than this. The effects of this dose of acepromazine were still apparent 6 hours after dosing and probably lasted for another hour. The data present a clear quantitative time course for a behavioral effect of acepromazine in the horse. It appears reasonable to suppose that this method can also be used to generate dose-response data for depressant drugs in the horse and it appears likely that the method will be applicable to other depressant drugs. Phenylbutazone and furosemide are widely used in racing horses and have been suggested by some authors to have overall calming or depressant effects on the behavior of horses.<sup>14,15</sup> They, too, were studied by observing their effect on the reliable locomotor response to fentanyl.

In early experiments on narcotic-tranquilizer combinations, several different combinations of acepromazine and morphine were investigated. As the dose of morphine was decreased and that of acepromazine increased, the peak of the locomotor activity was decreased by as much as 50%, as was the respiratory rate. Of the 4 horses in the experiment<sup>1</sup> (Fig 2), 2 stood still for periods up to 36 minutes, with their heads lowered almost to the floor and showing substantial sweating. The other 2 horses were less markedly depressed. The respiratory rate in these horses remained depressed for 4 hours, then was increased above base line for between 6 and 8 hours and had returned to control by 24 hours. Since morphine depresses respiration by reducing the sensitivity of the respiratory centers to CO<sub>2</sub>, the increased respiration between 6 and 8 hours presumably represents a "blowing off" of excess CO<sub>2</sub>.

Because naloxone is considered specific for narcotic receptors, the results presented here make it reasonable to assume that fentanyl, morphine, and pentazocine produce their locomotor stimulation by interacting with narcotic receptors.<sup>2,9</sup> Because the locomotor response is blocked by phenothiazine tranquilizers, its expression indicates involvement of other receptor systems, either adrenergic or dopaminergic. The ability of apomorphine, a relatively selective dopaminergic stimulant,<sup>7</sup> to stimulate locomotor activity in the horse<sup>13</sup> indicates that narcotic receptor activation causes dopaminergic stimulation which gives rise to the resultant locomotor response. Blockade of the locomotor response by acepromazine and haloperidol presumably takes place at the level of the dopaminergic receptor, and the blockade by haloperidol<sup>4</sup> is indicative of a dopaminergic site of blockade.<sup>7</sup>

As a practical matter, these results show that the locomotor response to narcotic analgesics is likely a direct function of the occupation of analgesic receptors, but also may involve a dopaminergic pathway.<sup>9</sup> They further reinforce the reliability and reproducibility of the fentanyl stimulation of locomotor activity and show how this response can be used to develop accurate and quantitative data on the actions of other depressant and tranquilizing drugs in the horse.

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