

# The Pharmacology of Narcotic Analgesics in the Horse. IV. Dose and Time Response Relationships for Behavioral Responses to Morphine, Meperidine, Pentazocine, Anileridine, Methadone, and Hydromorphone

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The behavioral and locomotor responses of the horse to intravenous doses of morphine, meperidine, pentazocine, anileridine, methadone and hydromorphone were examined. All of these drugs induced eating behavior at low doses, dose-related increases in locomotor activity as the dose was increased and incoordination at high doses. The locomotor effects were quantitated by the steps/2-minute method as described previously.<sup>1a</sup> High doses of morphine (2.4 mg/kg) intravenously (IV) yielded a motor response which peaked at about 100 steps/2-minutes three hours after dosing and then declined to control values over the next 11 hours. Hydromorphone (0.15 mg) produced a peak motor response of 30 steps/2-minutes which took 12 hours to return to control. Methadone, meperidine, and anileridine produced motor responses which peaked at about 30 minutes and lasted for about four, two and one hour, respectively. The locomotor response to pentazocine peaked at 30 steps/2-minutes, and the response was relatively short-lived. Comparison of the areas under the locomotor activity curves showed that morphine produced the most sustained and prolonged effects of any of the narcotics tested, up to 26 times greater than that of fentanyl and more than three times that of methadone, which produced the second greatest effect. No evidence for behavioral sedation or depression by low doses of most of these drugs was observed. Thus, all the narcotic analgesics tested stimulated locomotor activity in the horse, and it appears as though this effect is characteristic of the actions of narcotic analgesic drugs in the horse.

## Introduction

In a previous paper on the pharmacological responses to fentanyl and apomorphine, we showed that the locomotor response to these agents could be accurately and easily quantitated by a simple step-counting method.<sup>1a</sup> In this paper we have applied this method to measuring the locomotor responses to a number of different narcotic drugs by the horse. The experiments show that with small variations in the methods of collecting and handling data, because of the prolonged action of some of these drugs, this method is readily applicable to the study of all of the narcotic analgesics tested.

Application of this method to the study of the narcotic analgesics in the horse has allowed us to accurately quantitate dose- and time-response relationships for these drugs in the horse, and to demonstrate classic parallel log dose-response patterns for the locomotor response to these drugs. The results show that the potency of these drugs as locomotor stimulants in the horse closely follows their order of potency as analgesics in the human. However, the duration of effect, and thus the overall efficacy of these drugs as locomotor stimulants and presumably as analgesics, is markedly different from that observed in humans, with morphine clearly the most effective of the drugs tested. As well as observing and quantitating the locomotor effects of these drugs, we describe their ability to stimulate eating behavior at low doses and to cause incoordination at high doses.

#### Materials and Methods

Mature Thoroughbred and Standardbred mares and geldings, weighing 400 to 550 kg were brought into modified box stalls at least 24 hours prior to each experiment. The shielded stalls previously described<sup>14</sup> had a one-foot square glass window for observation of the horse. After IV administration of the appropriate drug or saline control, the observer recorded on a hand counter the number of steps taken by the horse and logged the cumulative score for each 2-minute period. A step was counted each time the horse lifted its left foot. Movements of the leg not resulting in relocation of the foot, such as scratching or pawing, were not counted. The reliability and reproducibility of this observational technique have been presented previously.<sup>14</sup> Clinical signs and behavioral characteristics were also noted throughout the experiments.

Water and grain buckets were removed from the stall prior to an experiment. Because eating behavior was early observed to be stimulated by the narcotic analgesics, hay was available to the horses in wall racks. Each horse was observed until its locomotor activity returned to control levels. This period ranged from 30 minutes for apomorphine to 14 hours for the highest dose of morphine tested. For drugs eliciting a locomotor response lasting over two hours, the horse was observed throughout the first two hours and then for the last 16 minutes of each succeeding hour. During experiments lasting over six hours, the horse was offered water immediately after each observation period.

Dose ranges for all drugs were tested from those that produced no observable behavioral stimulation to those that produced incoordination to the point at which an increase in dose might result in injury. At least six days was allowed between doses to reduce the possibility of sequential or tolerance effects. At all times during these experiments narcotic antagonists were readily available to counteract the effects of a narcotic overdose but their

Counts per two-minute period were plotted for all drugs, and the dose-response curves for fentanyl and apomorphine were plotted from Tobin *et al.* (1978).<sup>15</sup> For hydromorphone, methadone, anileridine, morphine, pentazocine, and meperidine, steps/2-minute period averaged per 16-minute time periods were determined, and these mean activities were used to construct the dose- and time-response curves. Results shown are the means of experiments involving from three to 10 horses, unless otherwise indicated.

Fentanyl citrate<sup>a</sup> was dissolved in saline 30 minutes prior to use. The other drugs used were apomorphine hydrochloride<sup>b</sup> (6 mg tablets dissolved in sterile distilled water immediately before injection); hydromorphone HCl injectable<sup>c</sup>; methadone HCl and morphine sulfate injectable<sup>d</sup>; anileridine HCl injectable<sup>e</sup>; pentazocine lactate injectable<sup>f</sup>; and meperidine HCl injectable.<sup>g</sup>

#### Results

In our initial report<sup>14</sup> on the step-counting method for quantitating the locomotor response to drugs, agents with intense but short-lived pharmacological effects were chosen. While the data generated by these agents were readily amenable to direct plotting as counts/2-minute period, application of this method to longer-acting narcotics turned out to be very laborious, both for collection of the raw data and its presentation. Figure 1 shows the locomotor response of an individual horse to increasing doses of morphine. At the two lowest doses tested (0.1 and 0.3 mg/kg), no substantial increases in locomotor activity were observed. At 0.6 mg/kg spontaneous locomotor activity gradually increased to peak at about 60 steps/2 minutes and then decayed away to reach control values after about four hours. If the dose of morphine was increased, the peak motor response was increased to about 80 steps/2 minutes (1.2 mg/kg) or to close to 120 steps/2-minute period at 2.4 mg/kg. At the high dose this rapid rate of response was maintained for almost eight hours, and then declined slowly to baseline, which took about 14 hours to reach in this particular animal. The experiment shows that the locomotor response to morphine tends to exhibit rapidly alternating peaks at low doses, but is quite prolonged and more stable at high doses.

Because of the prolonged and sometimes variable nature of the locomotor response to morphine, all counts for

<sup>a</sup> Gift of McNeil Laboratories, Fort Washington, PA.

<sup>b</sup> Eli Lilly Co., Indianapolis, IN.

<sup>c</sup> Wyeth Laboratories, Philadelphia, PA.

<sup>d</sup> Eli Lilly Co., Indianapolis, IN.

<sup>e</sup> Merck, Sharp & Dohme, West Point, PA.

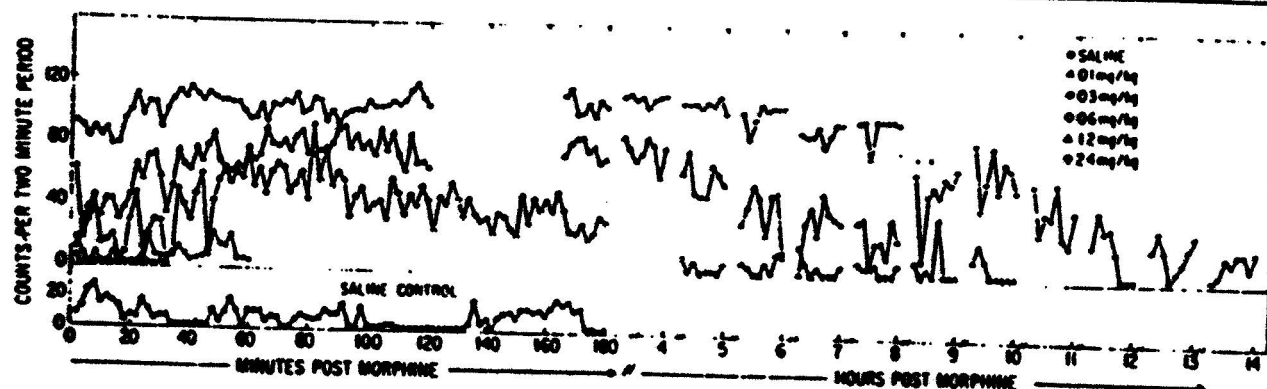


Figure 1. Effect of morphine on spontaneous motor activity in a single horse. A horse was injected<sup>1</sup> with saline and the indicated doses of morphine IV. The number of times the horse lifted its left front foot in each 2-minute period was recorded as an indication of motor activity. Activity following saline is shown by closed circles (●-●); 0.1 mg/kg morphine by open triangles (Δ-Δ); 0.3 mg/kg morphine by open circles (○-○); 0.6 mg/kg morphine by open diamonds (◇-◇); 1.2 mg/kg morphine by closed triangles (▲-▲); and 2.4 mg/kg morphine by teardrops (▽-▽).

16-minute periods were pooled and divided by eight to give a mean response for the standard 2-minute counting period. In addition, to reduce observer fatigue, horses were not continuously observed from four hours on, but only for 16-minute sample periods each hour. Figure 2 shows the pooled responses of four horses to the indicated doses of morphine. After 0.6 mg/kg, the peak motor response of about 30 steps/2-minute period occurred two hours after dosing. Doubling the dose to 1.2 mg/kg increased the response to about 50 steps/2 minutes, while doubling it again increased the mean response to about 90 steps/2-minute period. This response is close to the peak response observed to fentanyl in previous experiments (Tobin *et al.*, 1978). After 2.4 mg/kg, motor response to morphine decayed relatively slowly and required about 14 hours to return to baseline. An unexpected characteristic of the motor response to morphine, however, was the relatively slow onset of peak locomotor effect, taking up to three hours after IV administration of the drug.

In experiments not presented in Figure 2, horses dosed with 0.1 mg/kg morphine showed no increase in motor activity, and at 0.3 mg/kg four of five horses showed no increase in motor activity. At a dose of 0.6 mg/kg only one horse in four showed no increase in motor activity.

At the 1.2 mg/kg dose, all horses showed marked increases in motor activity and a markedly increased propensity to eat from their hay rack. Eating hay usually occurred early (first 90 minutes) and late (last four hours), while carrying hay in the mouth occurred during the period of greatest motor activity. At peak drug effect the horses still picked up the hay, "swiping" at it as they passed the hay rack, but were apparently unable to finish the process by chewing and swallowing it.

At the highest dose of morphine tested (2.4 mg/kg) all horses showed loss of coordination beginning about one hour (range 20-100 minutes) after dosing and continuing

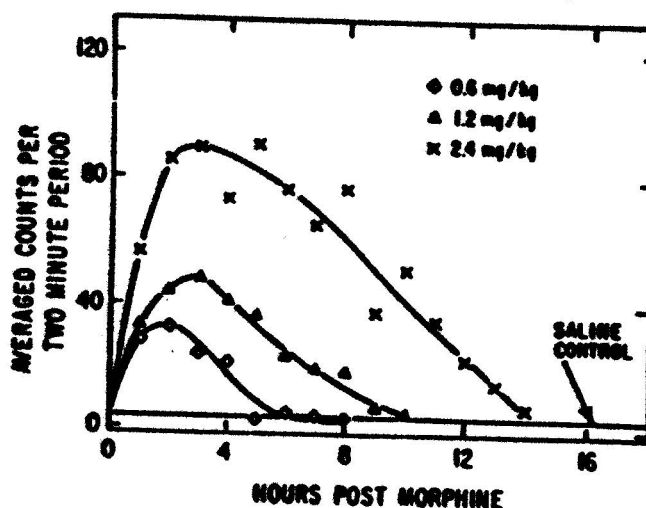


Figure 2. Effect of morphine on spontaneous motor activity in the horse. Horses were injected IV with saline and increasing doses of morphine. The average counts per two-minute period following saline injection are shown by the straight line near the bottom of the graph. The response to 0.6 mg/kg morphine 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-minute period were determined for the 16-minute interval immediately preceding the time indicated. All points are the means of such averaged counts on four horses.

up to seven hours. The horses walked as if oblivious to their surroundings until they slipped or bumped the wall, at which point they made appropriate corrections. If offered water, they appeared to play with it rather than drink. All horses ate large amounts of hay as their motor activity dropped from peak response to control values.

Since morphine is reported to cause central nervous system (CNS) depression and CNS excitation as a function of dose,<sup>1</sup> we carefully examined the effects of low doses of morphine and other narcotic analgesics on spontaneous activity in the horse. Table 1 shows the effect of low doses of morphine on the cumulative counts for the first 30 minutes after IV injection of 0.1 mg/kg morphine. The data show that after 0.1 mg/kg morphine, locomotor

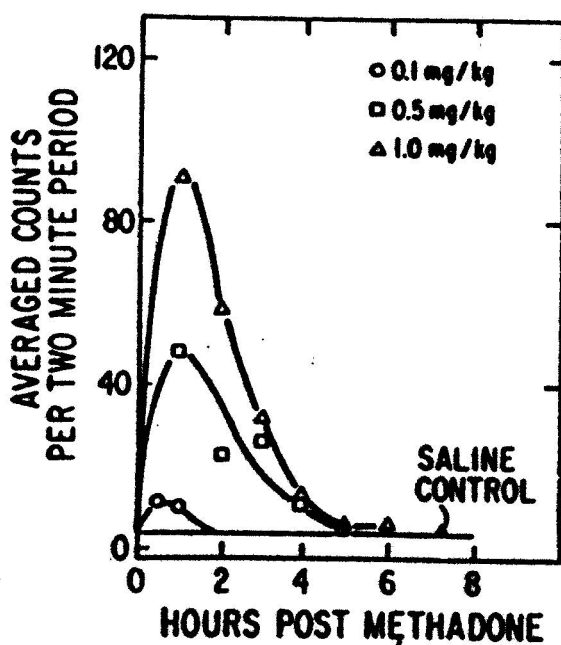


Figure 3. Effect of methadone on spontaneous motor activity in the horse. Horses were injected IV with saline or increasing doses of methadone. The average counts per 2-minute period following saline injection are shown by the straight line at the bottom of the graph. The response to 0.1 mg/kg methadone is shown by the open circles (O-O); to 0.5 mg/kg methadone by open squares (□-□); and to 1.0 mg/kg methadone by open triangles (Δ-Δ). Averaged counts per 2-minute period were determined for the 16-minute interval immediately preceding the time indicated. All points are the means of such averaged counts on four horses.

activity was apparently dramatically reduced, possibly suggesting a CNS depressant action of this dose of morphine.

(Observation of these animals, however, suggested that what was being observed was in fact an increase of eating behavior and thus, time spent at the hay rack, rather than a depression of spontaneous locomotor activity. To check this the experiment was rerun in a bare stall with no hay or straw present. Under these circumstances morphine did not reduce locomotor behavior, suggesting that the primary effect of these low doses of morphine was to stimulate eating rather than to depress motor activity. Similarly, low doses of fentanyl, pentazocine, methadone and apomorphine (all tested in the presence of hay) produced only small depressions in spontaneous motor activity.

Methadone is a synthetic narcotic analgesic with a particularly long plasma half-life ( $t_{1/2} = 15$  hours) in man.<sup>3</sup> Figure 3 shows the effects of increasing doses of methadone on locomotor activity in four horses. After IV methadone motor activity peaked within one hour and then declined, reaching control levels within five hours of administration at the higher doses. At the highest dose of methadone tested, all the horses were poorly coordinated, repeatedly bumped the stable walls and tended to go down. All horses also showed frequent urination (eight times in the first two hours at the high dose). Among the narcotics tested, methadone seemed particularly prone to cause incoordination, with signs being seen in two of the horses dosed with 0.5 mg/kg.

Pentazocine is another synthetic narcotic which is not at this time a Schedule II drug and is recommended by the manufacturer specifically for use in the horse. Figure

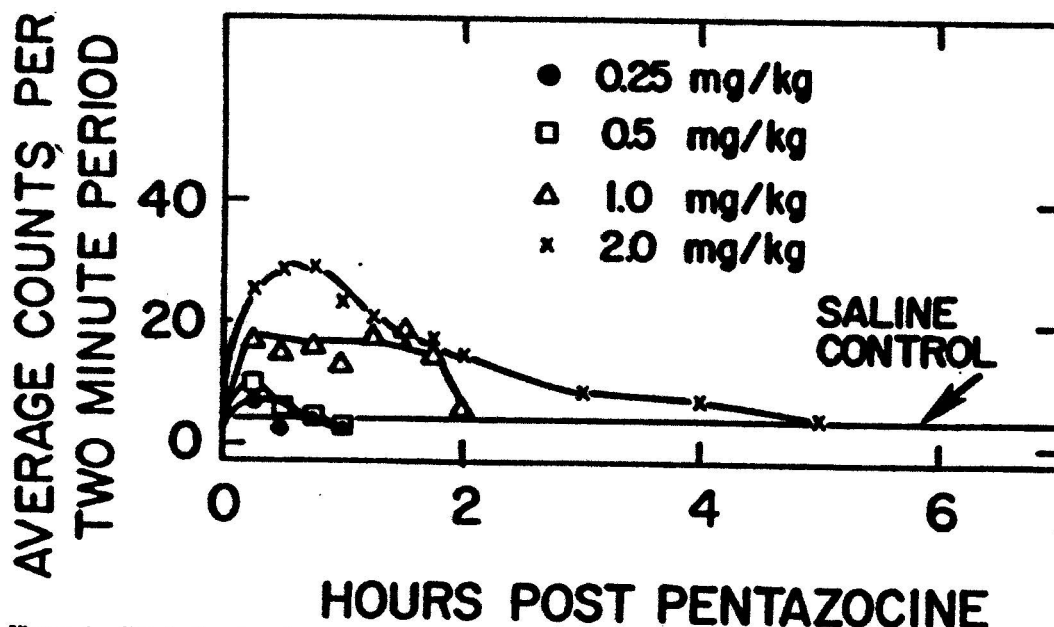


Figure 4. Effect of pentazocine on spontaneous motor activity in the horse. Horses were injected IV with saline or increasing doses of pentazocine. The average counts per 2-minute period following saline injection are shown by the straight line near the bottom of the graph. The response to 0.25 mg/kg pentazocine is shown by the closed circles (●-●); to 0.5 mg/kg pentazocine by open squares (□-□); to 1.0 mg/kg pentazocine by open triangles (Δ-Δ); and to 2.0 mg/kg pentazocine by crosses (X-X). Averaged counts per 2-minute period were determined for the 16-minute interval immediately preceding the time indicated. Points for the lower three doses are the means of such averaged counts on six horses. Ten horses were used for the 2.0 mg/kg dose.



4 shows the locomotor response observed after doses of pentazocine of up to 2.0 mg/kg. At the two lowest doses tested, little increase in spontaneous motor activity was seen, although a tendency to eat was noticed. At 1 mg/kg, three of the horses dosed showed signs of incoordination, and hay eating increased. At the highest dose tested (2 mg/kg) almost all the horses showed severe incoordination, some appeared reluctant to walk, and when they did, took very small steps. Of all the drugs tested, pentazocine produced incoordination which was associated with the smallest increase in locomotor activity.

A number of other synthetic narcotics were tested in this system, but without extensive replication. Small and

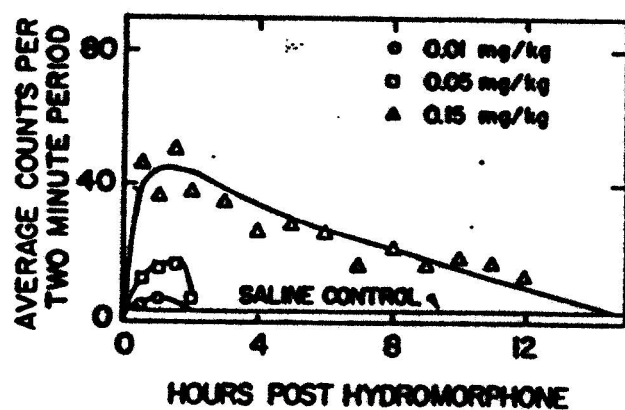


Figure 5. Effect of hydromorphone on spontaneous motor activity in the horse. A single horse was injected IV with saline or increasing doses of hydromorphone. The average counts per 2-minute period following saline injection are shown by the straight line near the bottom of the graph. The response to 0.01 mg/kg hydromorphone is shown by the open circles (O-O); to 0.05 mg/kg hydromorphone by open squares (□-□); and to 0.15 mg/kg hydromorphone by open triangles (Δ-Δ). Average counts per 2-minute period were determined for the 16-minute interval immediately preceding the time indicated.

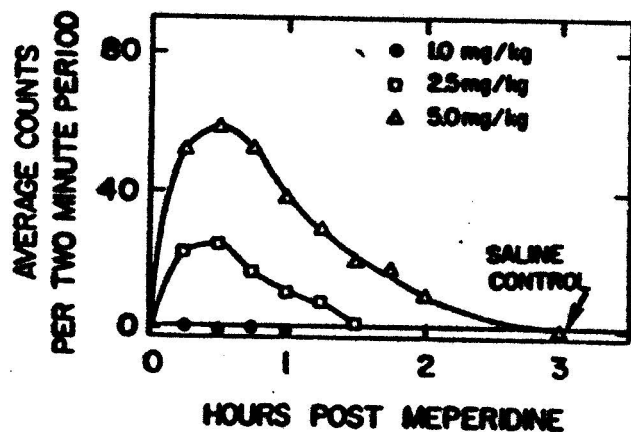


Figure 6. Effect of meperidine on spontaneous motor activity in the horse. A single horse was injected IV with saline or increasing doses of meperidine. The average counts per 2-minute period following saline injection are shown by the straight line near the bottom of the graph. The response to 1.0 mg/kg meperidine is shown by the open circles (O-O); to 2.5 mg/kg meperidine by open squares (□-□); and to 5.0 mg/kg meperidine by open triangles (Δ-Δ). Average counts per 2-minute period were determined for the 16-minute interval immediately preceding the time indicated.

transient responses to hydromorphone were seen at the two lowest doses tested, although a good hay-eating response was seen after 0.05 mg/kg (Figure 5). A good motor response, peaking at about 50 steps/2-minute period, was seen after 0.15 mg/kg. The horse showed a moderate loss of coordination at this dose during the first hour, and after this the motor response declined very slowly over the next 11 hours to control values, with steady hay eating observed throughout.

Meperidine (Figure 6) is a synthetic narcotic analgesic which has been recommended for use in the horse.<sup>11</sup> At the lowest dose tested (1.0 mg/kg) no increase in spontaneous locomotor activity or any other motor activity was seen. After 2.5 mg/kg a modest increase in locomotor activity was seen. At the highest dose tested a good locomotor response was seen, although the horse was initially (for the first 14 minutes) uncoordinated, shaking and immobile. The response to meperidine was relatively short-lived, peaking at about 30 minutes and returning to control by about three hours.

Anileridine (Figure 7) is another synthetic narcotic with a reputation for being a useful central stimulant in the horse. At the lowest dose tested (0.05 mg/kg) no motor effects were observed. A four-fold increase in dose to 0.2 mg/kg produced a small increase in motor activity. Increasing the dose to 0.8 mg/kg produced a good increase in motor activity with only slight incoordination and muscle quivering.

Figure 8 shows peak locomotor responses for each dose of these narcotic analgesics and apomorphine from

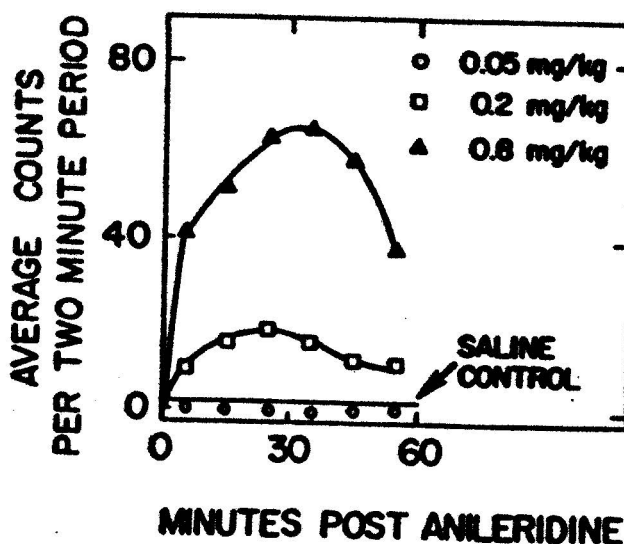


Figure 7. Effect of anileridine on spontaneous motor activity in the horse. A single horse was injected IV with saline or increasing doses of anileridine. The average counts per 2-minute period following saline injection are shown by the straight line near the bottom of the graph. The response to 0.05 mg/kg anileridine is shown by the open circles (O-O); to 0.2 mg/kg anileridine by the open squares (□-□); and to 0.8 mg/kg anileridine by the open triangles (Δ-Δ). Average counts per 2-minute period were determined for the 16-minute interval immediately preceding the time indicated.

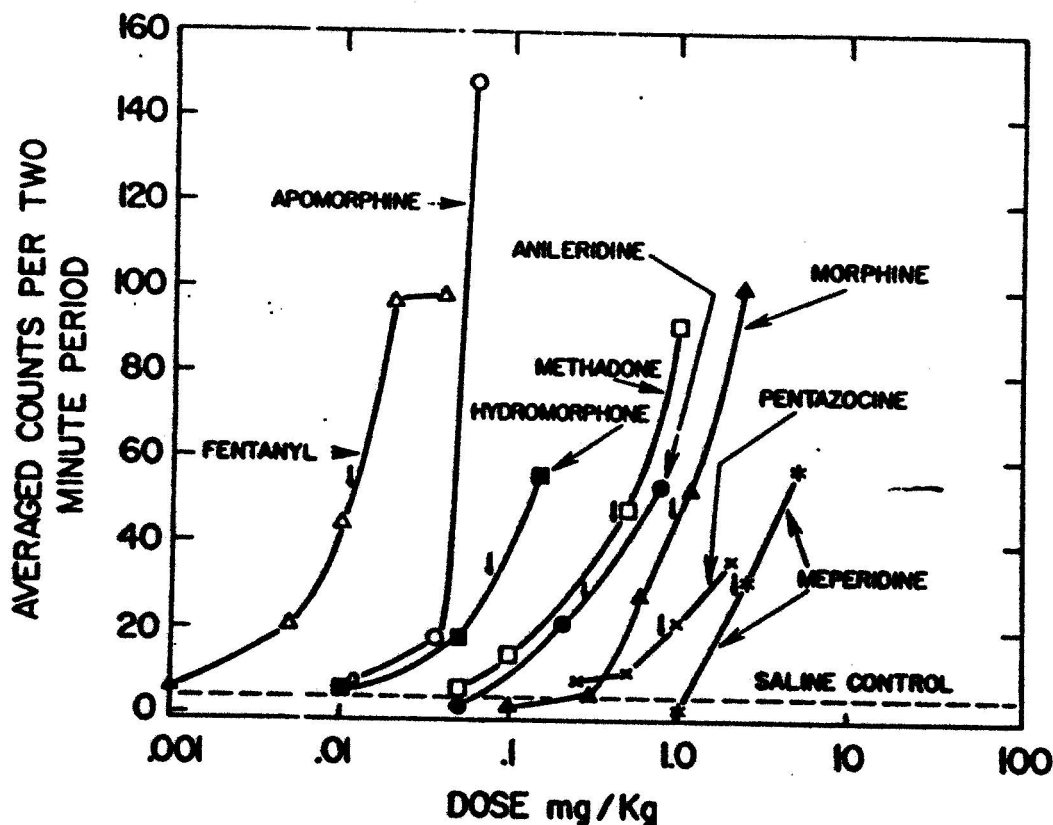


Figure 8. Dose-response curves for locomotor activity following narcotic analgesics in the horse. Horses were injected IV with saline and increasing amounts of the indicated drugs. The average number of steps taken during the peak 2-minute period were replotted for fentanyl and apomorphine from Tobin *et al.*<sup>10</sup> For all other drugs, average steps per 2-minute period were determined for the 16-minute interval of peak activity. Three to 10 horses were used in the experiments on fentanyl, apomorphine, methadone, morphine and pentazocine. One horse was used to determine the dose-response curves for each of hydromorphone, anileridine, and meperidine. The average counts per 2-minute period for the saline control are shown by the straight line at the bottom of the graph.

Tobin *et al.*<sup>10</sup> plotted as log dose-response curves to allow direct comparison of the potency and efficacy as locomotor stimulants of the various members of this group of drugs.

#### Discussion

In this report, the behavioral effects of a representative cross-section of the narcotic analgesics likely to be used in the horse were investigated. While the locomotor response was the quantitated response and provides the data base for this report, other behaviors were also apparent and are therefore described.

At the lowest doses tested the narcotic drugs appeared to stimulate eating behavior and, if the dose of drug was low enough, this was the principle behavioral effect seen. Saline controls for each drug, the smallest doses of morphine, apomorphine, pentazocine, methadone and the two lowest levels of fentanyl were analyzed using a Kruskal-Wallis test. The *p* value for the drugs was 0.19 and for the salines 0.8, showing no differences between drugs tested. The Wilcoxon one sample test was used to analyze the differences in induction of locomotor activity between the drugs and the saline controls.

By this test the only significant differences were observed for morphine with a *p* value of less than 0.002. However, observation of the animals suggested that the reason for lowered locomotor scores was that the animal stood in front of the hay rack and ate. This interpretation was tested by comparing the effects of a low dose of morphine with saline in a bare stall. Under these circumstances (Table 1) the Wilcoxon one sample test indicated no significant reduction in locomotor activity due to morphine. These experiments, therefore, show no evidence suggesting a general behavioral depression in the horse at any of the doses of the drugs tested on more than one horse. Insufficient data for a statistical analysis was gathered on anileridine, hydromorphone and meperidine.

This finding also illustrates the difficulty with such ill-defined and general terms as "stimulation" and "depression" when describing drug-induced responses. It is apparent that behavioral responses to drug administration are complex and dependent upon dose, time course of drug action, and the environmental conditions under which the drug is studied. Therefore, the observation of increases or decreases in the rate of a particular behavior

TABLE 1

Cumulative counts for first 30 minutes post-narcotic compared with counts post-saline.\*

Dose (mg/kg)	Drug	Counts Post-drug	Counts Post-saline	Number of Replicates	Statistical Significance
0.1	Morphine	28	83	9	p = 0.002
0.1	Morphine (bare stall)	73	83	4	
0.0005	Fentanyl	96	66	4	NS
0.001	Fentanyl	64	66	4	NS
0.25	Pentazocine	84	64	6	NS
0.05	Methadone	60	93	4	NS
0.013	Apomorphine	64	85	7	NS
0.05	Anileridien	3	19	1	—
0.01	Hydromorphone	72	71	1	—
1.0	Meperidine	6	19	1	—

\* Data from all drug and saline experiments replicated four or more times were analyzed using a Kruskal-Wallis test. The p value for the differences between drugs was 0.16 and between the saline G.R., showing no differences within these groups. Differences between the drugs and their groups were compared using a Wilcoxon one sample test. By this test significant differences were observed only in the first morphine test, with a p value of less than 0.002. No significant differences were observed between the other pairs.

drug as a general behavior or CNS stimulant or depressant.<sup>14</sup>

Though most apparent at low doses of these narcotics, the eating behavior tended to persist as the dose of the narcotic was increased and the locomotor response became dominant. Thus even at peak motor response those horses which remained well coordinated tended to snatch wisps of hay from the rack as they trotted past. Often at these high doses the horses held the wisps in their mouths for quite long periods and failed to eat them. The impression created by this behavior was that the horses had the desire to eat but were too busy running. However, as the locomotor response decayed, the animal's eating behavior increased, and some animals ate considerable amounts of hay as the locomotor effect of these drugs declined. It is believed by some charged with the care of racehorses that an injured horse should be given an analgesic (fentanyl has specifically been suggested) to prevent the horse from going off its feed. Presumably, the rationale for this practice is that blocking the pain will allow the horse to eat normally. From our experiments, it appears clear that the narcotic analgesics have a direct effect on eating behavior, which would account for these observations. In the horse, stimulation of eating may be analogous to the stereotyped gnawing and biting seen in rats and other species after injections of morphine.<sup>3</sup> Such effects are often attributed to the dopaminergic effects of opiates.<sup>2,15</sup>

In all of these experiments the dose of the narcotic was increased until doses producing incoordination were reached. As pointed out previously, incoordination was not observed with apomorphine, so incoordination is possibly associated with interaction with narcotic receptors.

In support of this hypothesis is the observation (Combie *et al.*, in preparation) that small doses of naloxone administered during the peak motor response to morphine completely inhibited incoordination in these horses over the remaining time period of the experiment, while only transiently depressing motor activity. These observations support the idea that the incoordination produced by high doses of narcotic analgesics is mediated via their activity on opiate receptors.

The effects of morphine in the horse are similar to those seen in nontolerant rats. Doses of 2.5 mg/kg or less increase locomotor activity, eating, drinking, gnawing and grooming behavior.<sup>16</sup> Higher doses (< 10 mg/kg) produce an initial catalepsy and a decrease in respiration, which is later followed by the increased locomotor behavior and gnawing observed at lower doses. This sequence of behaviors is therefore monophasic at low doses and biphasic at higher morphine doses. Our results suggest that the reduced mobility and incoordination observed in horses at the highest opiate doses represents the onset of motor effects similar to the rigid catalepsy observed in rats. These cataleptic effects in rats are antagonized by naloxone and dopaminergic agonists, while the locomotor stimulant effects are antagonized by catecholamine depleters and dopamine blocking agents.<sup>17</sup>

Among the different narcotics, incoordination occurred most readily with pentazocine, becoming dominant after the relatively small increase in locomotor activity of about 30 steps/2-minute period. At this dose, many of the horses were so severely incoordinated that they appeared reluctant to walk. This relatively low efficacy of pentazocine as a locomotor stimulant agrees well with what is known about its pharmacological characteristics

at the molecular level. Pentazocine is a molecule which has been specifically selected as one with a mixture of agonist (*i.e.*, narcotic analgesic) characteristics and antagonist characteristics.<sup>14</sup> Because of these characteristics, the molecule is unable to produce the equivalent of more than partial activation of the narcotic receptors, and thus its locomotor effects and presumably its analgesic efficacy are limited.<sup>14</sup>

In contrast to pentazocine, fentanyl, morphine and methadone all produced substantial locomotor effects (about 100 steps/2 minutes) before incoordination became limiting. It appears likely that this figure represents the maximal locomotor activation that may be produced by any narcotic under our experimental conditions, since these agents are all potent and relatively specific narcotic agonists. In contrast, the limited data available for hydromorphone, unilertidine and meperidine suggest that incoordination occurred more readily with these drugs than with fentanyl or morphine. However, firm conclusions on this effect are limited by the amount of experimental data available. A schematic representation of the interplay of these three behavioral responses to the narcotics is presented in Figure 9.

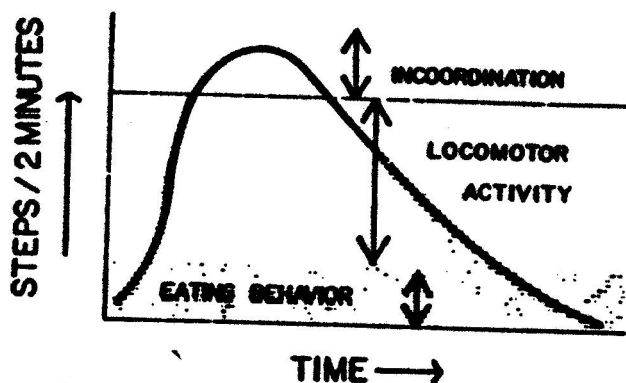


Figure 9. Schematic representation of relationships among narcotic-induced behaviors in the horse. The solid line represents a typical locomotor activity response to a large dose of a narcotic drug in a horse. At lower dose rates, or at the beginning or end of a response, eating behavior predominates. As the dose of drug, and presumably its plasma levels increase, locomotor activity becomes predominant, with traces of eating behavior remaining. At very high doses of drug (and therefore plasma levels), incoordination becomes dominant and limits the motor response.

The relative potency of these various narcotic analgesics in inducing locomotor activity is presented in Table 2, and appears broadly similar to the analgesic potency of these drugs reported in man. Kosterlitz and Waterfield<sup>15</sup> rank these agents for relative potency in man in the order of meperidine, pentazocine, morphine and methadone, the same order in which they rank in Figure 8. Similarly, fentanyl is reported to be 80 times more potent than morphine in man, which is in good agreement with the 82-fold difference observed in Table 2.<sup>14</sup> From these data, it appears that the relative

In addition to the broad differences in potency observed in these experiments, there are considerable differences in the time courses of the locomotor responses to the narcotic analgesics and their potency on the basis of the period for which effective analgesia was induced. Thus, after fentanyl (Tobin *et al.*, 1978) the peak motor response was observed within three to four minutes of injection, and the effect was over within 60 minutes. On the other hand, the pharmacological effects of morphine took up to three hours to peak after IV administration and lasted for up to 14 hours. These differences in time course of drug effect probably reflect pharmacodynamic and kinetic factors as well as differences in intrinsic activity. The delayed onset of morphine-effect relative to fentanyl, methadone and hydromorphone is consistent with its relatively low lipid solubility which accounts for the slowness with which morphine gains entry to and is eliminated from the CNS. However, the relative durations of action of these compounds (morphine > hydromorphone > methadone > fentanyl), at doses which produce roughly the same peak effect, are poorly correlated with their heptane/water partition coefficient.<sup>16</sup> Therefore, drugs with long durations of action may indicate very slowly declining brain and plasma levels and thus a long plasma and urinary half-life for these drugs and their metabolites. At this point, however, no kinetic data on the plasma and urinary half-lives of either morphine or hydromorphone in the horse are available to compare with this behavioral data.

All of the other drugs tested had actions which were relatively brief compared with the prolonged actions of morphine and hydromorphone. Meperidine has a relatively short action in the horse, with most of the locomotor effects over within 2 hours after 5.0 mg/kg. This brief action of meperidine is in good agreement with the relatively short plasma half-life in the pony of 66 minutes reported by Alexander and Collett.<sup>17</sup> It appears unlikely, therefore, that at the usually used doses of meperidine its analgesic action will last for more than two hours.

The duration of the response to pentazocine was also short. The manufacturer's recommended dose of pentazocine in the horse is about 0.3 mg/kg, less than the 0.5 mg/kg dose which produced very little effect in our hands. A 1.0 mg/kg dose produced a modest (less than 20 steps/2 minutes) increase in motor activity for about two hours, while 2.0 mg/kg produced a peak response of 30 steps/2 minutes, which declined to control over the next few hours. These results are in good agreement with the results of Lowe *et al.*,<sup>8,10</sup> who report no analgesia in an equine colic model at 1.1 mg/kg pentazocine. These observations suggest that minimal pharmacological response to the manufacturer's recommended dose of pentazocine may be expected. From the data reported here and that of Lowe *et al.*,<sup>8,10</sup> the effectiveness of pentazocine

Methadone yielded a brisk but brief locomotor response in the horse, with peak activity of about 90 steps/2 minutes occurring about one hour after its IV administration. The time course of methadone's action was relatively brief, with the pharmacological response being complete within four hours. The data suggest that methadone is likely to produce useful analgesia in the horse over a relatively short (3 hours) period of time. This relatively brief action of methadone in the horse is in contrast with its relatively prolonged action in man, in whom it is used as a long-acting substitute for heroin in addicted patients.<sup>8</sup> However, the duration of analgesia in rabbits is shorter after methadone than after an equipotent dose of morphine, suggesting that species differences are important.<sup>9</sup>

As a practical matter these results suggest that the clinical efficacy of narcotic analgesics in the horse are different from those observed in man. This is because if the areas under the locomotor activity curves are taken as an indication of the response of the horse to these narcotic drugs (Table 2), morphine is clearly the most effective drug, with a 26-fold greater area under the curve than fentanyl, and a three and one-half-fold greater area under the curve than methadone. These observations suggest that for a prolonged response to a narcotic drug in the horse, morphine is the drug of choice,<sup>10</sup> while for a short, sharp response to a narcotic drug, fentanyl is the drug of choice.

The final questions raised by these experiments are how the analgesic actions of these drugs relate to this

TABLE 2

ED<sub>50</sub> for narcotic analgesics on locomotor activity in the horse.

Drug	ED <sub>50</sub> mg/kg	Ratio of ED <sub>50</sub>	
		Fentanyl = 1	Ratio of areas under curve Fentanyl = 1
Fentanyl	0.011	1.0	1.0
Hydromorphone	0.08	7.2	2.6
Anileridine	0.27	24.0	1.6
Methadone	0.42	38.0	7.4
Pentazocine	0.80	72.0	1.6
Morphine	0.91	82.0	26.0
Meperidine	1.11	100.0	2.5

locomotor effect and whether or not the locomotor effects can be specifically blocked to enable utilization of the analgesic effects of these drugs in the horse. As pointed out previously, the time course of analgesic response to fentanyl in man corresponds almost exactly with the time course of the motor response to fentanyl in the horse, suggesting a close correlation for this particular drug.<sup>11</sup> The correlation for pentazocine also appears good, in that both the motor response and the analgesic response to the drug are poor and require relatively high doses of drug. With regard to blockade of the motor response, it appears relatively clear now that the motor response to narcotic drugs is dopaminergic in origin,<sup>12</sup> and experiments in progress suggest that it should be relatively easy to block expression of the motor response to these drugs.

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