

Pharmacology Review: Actions of Central Stimulant Drugs in the Horse II.

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Apomorphine

Apomorphine is obtained from morphine by treatment with a strong mineral acid, which causes substantial rearrangement of the molecule (Figure 1). These changes result in a loss of the analgesic properties of morphine and in the appearance of pharmacological activity resembling the actions of the neurohormone dopamine.³ Apomorphine is now thought by most authorities to be a pure dopaminergic agonist, i.e., a drug whose effects mimic the actions of dopamine and directly stimulate dopaminergic receptors. Despite some comments in a recent textbook of pharmacology,⁶ apomorphine is not thought to have any significant effects on narcotic receptors, and its pharmacological effects in the horse are certainly not antagonized by naloxone, a specific blocker of narcotic receptors (see Figure 5).

In man, the pharmacological activity of apomorphine appears as activation of the chemoreceptor trigger zone (CTZ) and stimulation of vomiting, which has been its principal use in human and small animal medicine. However, in some animals, and particularly in the horse, apomorphine is a powerful locomotor stimulant which induces a very specific pattern of locomotor activity. This locomotor-stimulating action of apomorphine has been studied extensively in small laboratory animals,^{3,11} and we have recently extended these studies to the horse.

Apomorphine produces its motor stimulant actions by directly stimulating dopaminergic receptors. Cell groups located in the mesencephalon give rise to most of the ascending neurons which contain dopamine. These neurons terminate in the striatum, the limbic system, and the cortex. These cells fulfill all the criteria for dopaminergic neurons in that the necessary machinery to synthesize, store, and release dopamine are present in them. Apomorphine acts to mimic the action of naturally released dopamine at its postsynaptic receptors, and it is this direct receptor activation which gives rise to its pharmacological effects.

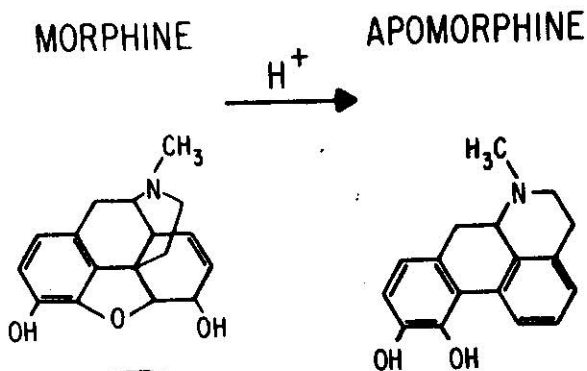


Figure 1. Structural formulae of morphine and apomorphine.

The role of dopaminergic receptors in the stimulation of locomotor activity has been very neatly demonstrated in a series of experiments by Moore and co-workers.¹¹ In these experiments Moore lesioned the dopaminergic tracts on one side of the brain in mice and waited a few days for the surgical (but not the neurological) lesions to heal (Figure 2). They then dosed these animals with amphetamine. Amphetamine, as indicated previously,¹⁴ produces its central pharmacological effects by stimulating the release of norepinephrine and dopamine from nerve terminals. However, since the lesioned mice had intact dopaminergic tracts on only one side of the brain, dopamine was released and acted only on this intact side. The result was that locomotor activity was stimulated on one side of the brain only, and these animals

DOPAMINERGIC STIMULATION OF TURNING BEHAVIOR IN MICE

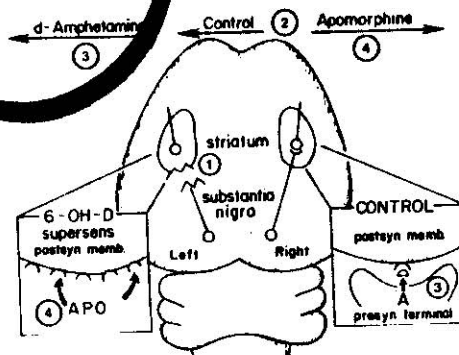


Figure 2. Unilateral locomotor stimulation in mice by apomorphine and amphetamine.¹¹ Dopaminergic neurons in the brain are lesioned on the left side (1) and a period of a few days allowed. Because dopamine is now only released on the right side of the brain, these animals are only stimulated to run on this side and thus, spontaneously circle to the left (2). If amphetamine is administered it can stimulate dopamine release only on the right side and the animal turns faster to the left (3). If apomorphine is given, it finds more dopaminergic receptors which have developed on the left side to directly stimulate (4), so the apomorphine-stimulated mouse circles the other way (4).

were therefore running faster on one side than the other. This, as horsemen are well aware, leads to turning, and Moore simply counted the number of circles which the mice made to get a measure of the response to amphetamine (Figure 2).

If apomorphine was administered to these animals, however, they turned just as fast in the opposite direction. The reason for this is that when the dopaminergic tracts were lesioned, release of dopamine from the lesioned fibers ceased. The first response of the receptors under this circumstance was to increase in number, in an attempt to increase their sensitivity to dopamine. When apomorphine was given to these mice, it found more receptors to stimulate on the lesioned side than on the normal side. Since apomorphine is a direct receptor agonist, these animals were therefore more stimulated and ran faster on the lesioned side. The experiment pinpoints the different mechanisms of action of amphetamine and apomorphine, and makes quite clear the direct action of apomorphine on dopaminergic receptors.^{3,11}

One can imagine that if apomorphine is a direct locomotor stimulant in mice, that its effects in Thoroughbred horses are likely to be dramatic, and

this is usually the case. While horses, for reasons which are not clear, do not respond reliably to apomorphine, when they do respond the effect is dramatic. As shown in Figure 3, 6 mg of apomorphine in a 1000 lb horse can produce a sharp increase in locomotor activity.¹⁶ Increasing the dose can increase this up to about 160 steps/2-minute period, or 80 steps/minute. Peak locomotor activity occurs at about five to six minutes after an intravenous (IV) dose and declines rapidly thereafter. By 40 minutes postdosing all of the horses tested had returned to baseline locomotor activity of about 4 steps/2-minute period and were apparently normal. Apomorphine is a very potent drug in the horse, and a dose of less than 0.1 mg/kg (50 mg) produces a locomotor stimulation of up to 40 times the normal motor activity. The dose response curve to apomorphine can also be unusually steep, as shown in Figure 4.

While the apomorphine produces a locomotor stimulation which closely resembles that produced by the narcotic analgesics,^{2,16} there are a number of characteristic differences between the actions of these drugs. Apomorphine-treated horses remained well

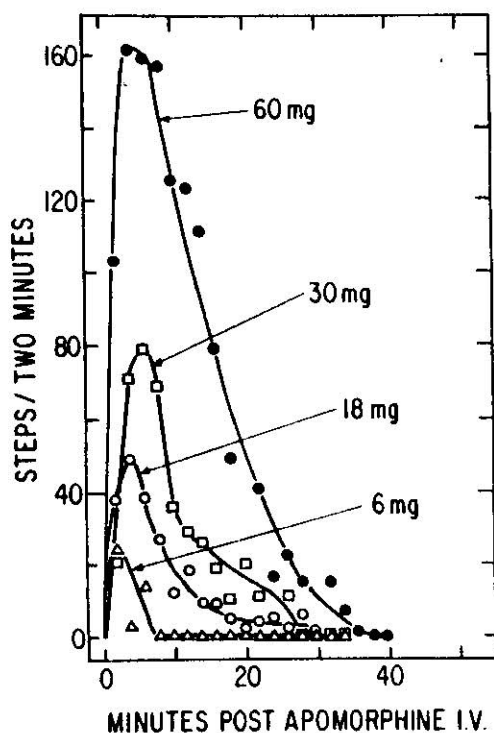


Figure 3. Effect of apomorphine on spontaneous locomotor activity in the horse. A horse was injected intravenously with either 6 (Δ - Δ), 18 (\circ - \circ), 30 (\square - \square), or 60 (\bullet - \bullet) mgs of apomorphine. The symbols represent the number of steps/2-minute period postinjection, measured as described by Tobin et al.¹⁶

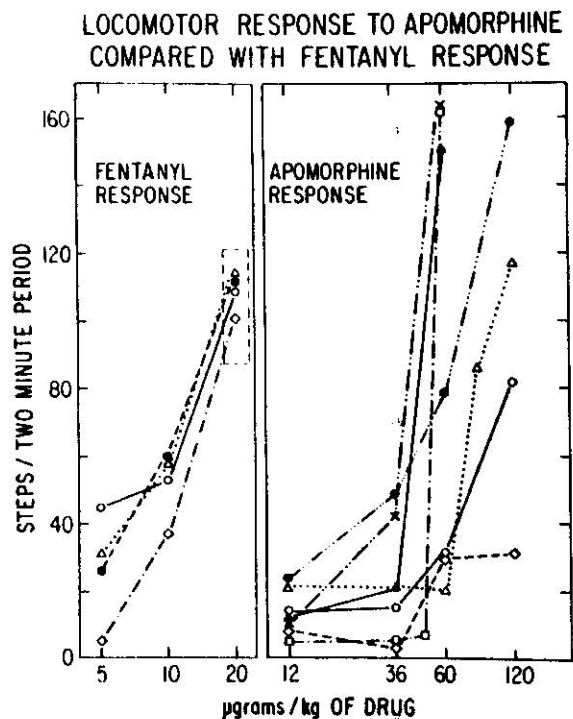


Figure 4. Individual dose response curves to fentanyl and apomorphine in the horse. The left-hand panel shows four individual dose-response curves to fentanyl obtained in a sequence of experiments. The consistent nature of the response to fentanyl is indicated by the dashed window and has been seen repeatedly in other experimental work.^{2,16} The right-hand panel shows all the dose-response data obtained with apomorphine, demonstrating the wide scatter in responses and the sometimes very steep dose-response curves obtained with apomorphine.

coordinated at all doses tested, and the dosages used were limited only by the animal's ability to maneuver at speed in the confines of a box stall. On high doses of apomorphine our horses "got up" to rates of 160 steps/2-minute period, at which point they were moving as rapidly as they could in the stall. In contrast, as the dose of fentanyl was increased and the horses surpassed rates of about 100 steps/2-minute period, they showed a slight impairment in coordination and occasionally bumped into the walls of the stall. If the dose of fentanyl was further increased, the animals became incoordinated and fell.¹⁶ This incoordination was a direct effect of the fentanyl and not due to the small size of the loose boxes, because animals on apomorphine gave much greater locomotor response with no signs of incoordination.

Unlike the dreamy, dissociated appearance of animals on high doses of narcotics,² horses on apomorphine appeared apprehensive and uncomfortable with the presence of the observer. While horses on fentanyl circled, horses on apomorphine always kept a distance from the observer. Locomotor activity on apomorphine invariably took place along the wall of the box distant from the observer, the horse paced back and forth repeatedly. If the animal was extremely excited and apprehensive, it lunged up toward the ceiling as it reached each corner, as though seeking to escape out of the loose box over the far corner. At this point it would abruptly change direction, pace back along the wall to the other distant corner of the box and repeat the process. All these maneuvers were carried out at speed, as the pacing rate of up to 80 steps/minute suggests, and the horses were well coordinated throughout. If the dose of apomorphine was further increased, the horses tended to injure themselves on the loose box walls.

In addition to these remarkable increases in locomotor activity, horses dosed with apomorphine emitted a typical snort or snore during the period of drug action. This sound was so characteristic it came to be referred to in the laboratory as the "apomorphine snort." This same snort has been reported and commented on by Mackay.⁹ Although horses dosed with narcotic analgesics showed many behaviors suggestive of dopaminergic stimulation, they never emitted this typical "apomorphine snort."

Another characteristic of the apomorphine response which became apparent as the experiments progressed was unreliability. While the locomotor response of horses to fentanyl was always highly predictable and repeatable within 90 minutes, the response of any horse to apomorphine could never be predicted or reliably repeated. As shown in Figure 4

and seen repeatedly in other experimental work,^{1,13} the peak response to fentanyl was always found at 20 $\mu\text{g}/\text{kg}$ and was always very close to 100 steps/2-minutes. On the other hand, a peak response or no response to apomorphine might be found after doses of between 18 mg and 30 mg, while on occasion, about 60 mg was not enough to elicit more than a small response. The reasons for these highly erratic responses to apomorphine are not clear, but these responses apparently also occur in the human, where it is reported that if the first dose of apomorphine does not induce emesis, subsequent doses are even less likely to do so. It would therefore appear that the variability in response to apomorphine which we have observed in the horse occurs also in other species.

As with fentanyl, the onset of action of apomorphine in the horse is very rapid (Figure 3), so it appears likely that apomorphine is also a highly lipid-soluble drug which enters the brain rapidly. The decline in the effect of apomorphine, however, can also be very rapid, and the decline may be too rapid to be readily accounted for by redistribution. The locomotor response to fentanyl, which peaks even more rapidly than the response to apomorphine, invariably declines in a slow exponential fashion,^{2,16} whereas the response to apomorphine can decline from 130 to 5 steps/2 minutes within minutes (Figure 5). Since apomorphine is very susceptible to oxidative degradation, it may be that oxidation of this drug as it distributes *in vivo* can account for its variable effectiveness and the sometimes very rapid decline in its pharmacological response.

As pointed out previously, conversion of the morphine molecule to apomorphine converts it from a narcotic drug to a dopaminergic agonist. The pharmacological effects of apomorphine are therefore not

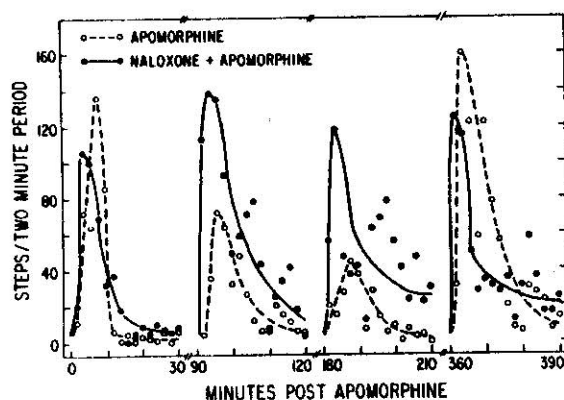


Figure 5. Lack of effect of naloxone on apomorphine-stimulated locomotor activity. The open circles (○—○) show the locomotor response of a single horse to repeated doses of 30 mg apomorphine IV. The solid circles (●—●) show the locomotor response in horses pretreated with naloxone, 0.015 mg/kg.

sensitive to narcotic antagonists such as naloxone (Figure 5). Indeed, inspection of the data of Figure 5, which shows the variable nature of the response to repeated doses of apomorphine alone, suggests that, if anything, the apomorphine response is more consistent and reliable in the presence of naloxone. This experiment is again in contrast with the actions of fentanyl, whose highly repeatable responses are specifically blocked by small doses of naloxone.²

The locomotor response to apomorphine in the horse is blocked by butyrophenone tranquilizers such as haloperidol and is also likely to be blocked by phenothiazine tranquilizers such as acepromazine. In studies on the pharmacokinetics of apomorphine in the horse, Miller¹⁰ routinely dosed horses with 90 mg apomorphine in an attempt to obtain consistently measurable blood levels of apomorphine. All these animals were pretreated with 15 mg of haloperidol, and no difficulty in handling or obtaining blood samples from any of these horses was experienced.

Plasma levels of apomorphine, however, were difficult to detect reliably. In horses dosed with about 90 to 100 mg of apomorphine, Miller¹⁰ found plasma levels of apomorphine of about 25 ng/ml or less, and plasma levels of the drug tended to be erratic. Urinary levels of the drug could not be successfully quantitated but Maylin⁹ reports detection of apomorphine in equine urine for up to 48 hours after its IV administration. Apomorphine is excreted in equine urine at least partly as a glucuronide metabolite, which may be expected to persist in urine for at least 48 hours after dosing and be quite susceptible to dilution by diuretics such as furosemide.

These authors are not aware of any published work on apomorphine in the horse other than by Mackay,⁹ any clinical uses for apomorphine in the horse, or any studies in which this drug has been used in performance trials. Until recently, apomorphine was classified with morphine as a Schedule II drug, but is no longer so classified.

Pemoline

Pemoline is a central nervous system stimulant which is structurally distinct from the amphetamines and methylphenidate. It is poorly soluble in water, which creates problems with its IV administration. In our experiments with pemoline, we chose to make it up for IV injection in dimethylsulfoxide, in which pemoline is relatively soluble.

Pemoline has been shown to stimulate locomotor activity in small laboratory animals at doses of about

10 mg/kg. In preliminary experiments in horses, small increases in motor activity were seen with doses of up to 2 g/1000 lbs IV. At these doses, the horses showed clear-cut signs of stimulation, were restless, wandered about the stall, and constantly searched along the stable floor for food. While these signs are suggestive of low levels of dopaminergic stimulation in the horse, administration studies with higher doses of drug need to be performed.

In studies on the effects of drugs on performance of horses, Sanford¹⁴ showed that pemoline significantly ($P < 0.05$) increased speed over a 200-meter gallop test at doses of 4 g/horse by an unspecified route. No details on times or percent improvement in performance were presented. Nevertheless, it seems clear that pemoline is a potential performance-improving drug in the horse, although the doses required to produce these effects are extremely large compared with those of other CNS stimulants.

No data on the metabolism or urinary "clearance times" of pemoline in the horse are currently available.

Caffeine

Like most plant drugs, mankind has known about caffeine since earliest times, and use of caffeine in tea, coffee, and soft drinks is widespread throughout the world. Caffeine has an unusual position in sports medicine in that its use is permitted in human athletes if it is taken as a beverage, but not if it is taken in an abnormal way or in abnormal amounts. No such distinction is made in horse racing, however, and traces of caffeine or any of its metabolites in equine urine can cause many problems if reported by an analytical chemist.

The precise mode of action of caffeine is not clear, but it appears reasonably certain that its site of action is both postsynaptic and intracellular. Caffeine appears to act by potentiating the actions of norepinephrine, most likely via its action on a substance called cyclic AMP. When norepinephrine activates its postsynaptic receptors, its effect is to increase the level in the postsynaptic cell of cyclic AMP. This second messenger, cyclic AMP, is, in turn, broken down by an enzyme called "phosphodiesterase." It turns out that caffeine inhibits these phosphodiesterase enzymes and causes increased levels of cyclic AMP in the postsynaptic cell. The effects of a dose of caffeine are thus equivalent to an increase in the amount of norepinephrine at the postsynaptic receptors, which leads to a general central nervous system stimulant effect.⁶

Studying the effects of caffeine on cardiovascular parameters in humans, Robertson and co-workers¹³

* Maylin, G. Personal communication, Cornell University, Ithaca, New York

found that 250 mg caffeine administered orally increased the respiratory rate and systolic and diastolic blood pressure. Only small changes in heart rate were seen. Plasma levels of the stimulatory neurohormones epinephrine and norepinephrine increased sharply after caffeine and remained elevated for the three hours of the experiment. Urinary volume was also increased in all subjects, with an increase of about 30% above control being observed. Since caffeine has a plasma half-life of between four and 10 hours in man, these effects can persist for quite some time in the human, accounting for the difficulty which some people may have sleeping after even modest amounts of coffee.

In studies on the effects of caffeine on three Thoroughbred horses, Fujii and co-workers⁴ injected horses with 2.5 g and 5 g (between 5 mg/kg and 10 mg/kg) of caffeine and sodium benzoate. These workers found that caffeine enhanced the running performance of all horses, especially at the canter, and that the amount of stimulation observed made it difficult to monitor motor activity on the small track available. In one horse atrioventricular (AV) and sinoatrial (SA) blocks were seen after caffeine, and in all horses caffeine increased the heart rate after exercise and delayed return of the heart rate to normal. The authors interpreted these results to indicate that caffeine markedly enhanced the running performance of horses, but tended to increase the frequency of cardiac arrhythmias.

In agreement with Fujii's work on performance, Sanford¹¹ found that caffeine, at 2 mg/kg, 4 mg/kg, and 8 mg/kg, increased speed significantly ($P < 0.05$) in gallop tests.

The metabolism and elimination of caffeine in the horse has been studied most extensively in England, where the inclusion of cocoa husk in horse rations has given rise to a number of inadvertent and embarrassing drug positives. Following administration of 3 g of caffeine orally, about 3% of the dose was excreted unchanged in the urine in the first 24 hours. Moss and Horner¹² found that about 1% of a dose of radiolabeled caffeine was excreted unchanged in the urine. Excretion took about three days to complete and 60% of the total radioactivity was excreted in the urine. Theophylline and theobromine each represented about 10% of the urinary radioactivity, and three polar metabolites were also found. No evidence for conjugation as either glucuronides or arylsulfates was found, but traces of theobromine sufficient to "call a positive" were found in horse urine for up to 10 days after a dose of caffeine.

Theobromine

As well as being a metabolite of caffeine, theobromine is also a drug in its own right, having a small diuretic action. Theobromine, along with salicylate, is one of the major constituents of a popular backache pill.⁶ These pills have been a favorite prerace medication of some trainers, presumably because of their salicylate (aspirin) content. When a chemist picks up a theobromine "positive" in the absence of caffeine, the chances are that it was given as theobromine. Since theobromine is virtually devoid of CNS or cardiovascular actions, its presence in urine is not likely to be a factor in influencing the outcome of a race.

Camphor

Camphor (d-camphor) is the chief constituent of oil of camphor and is obtained from the wood and bark of *Cinnamomum camphora* which is grown in Japan and Taiwan. Camphor was once used in human medicine as both a "cerebral" and respiratory stimulant, but these uses are now considered obsolete. Camphor, however, is still widely used in equine track practice as a respiratory stimulant, and Fujii and co-workers have studied its pharmacology in the horse in some detail.⁵ These authors considered camphor to be a cardiac stimulant and reported that it is commonly detected in postrace testing in Japan.

In their studies, Fujii *et al.* administered trans-oxy-camphor in 200 mg and 2000 mg doses IV to horses. They saw no behavioral changes in these horses, with the exception of tonic extensions of the head and neck in one horse immediately after a 2000 mg injection IV. Regardless of the dose of oxy-camphor administered, this drug did not appear to affect the speed of the horse. Oxy-camphor, however, tended to decrease the heart rate both during and after exercise. It prolonged the P-R interval in these horses and caused it to fluctuate greatly, in combination with double AV blocks. Reviewing the results of their experiments, Fujii *et al.* concluded that the actions of oxy-camphor that they observed in the horse suggested myocardial intoxication due to this drug. It appears that camphor in the horse is not likely to have any useful stimulant actions, and its therapeutic standing in equine medicine should probably be equivalent to that accorded it today in human medicine.

Cocaine

Cocaine is a plant alkaloid obtained from the leaves of *Erythroxylon coca* and related species. These

⁶ Doan's Pills. Purex Corporation, Batavia, IL.

plants are indigenous to Peru and Bolivia, where their leaves have been used for centuries for their stimulant effects. Cocaine has local anesthetic effects, as well as its central stimulant actions, and was the first local anesthetic to be introduced into medicine. However, because of its toxicity and addicting properties, cocaine was soon supplanted as a local anesthetic by the more specific and less toxic procaine. Later, after a period during which cocaine was a common additive in wines and soft drinks, it was quite incorrectly declared a narcotic drug, which remains its current legal classification.⁶

Cocaine produces its central stimulant effects by specifically blocking the pump which moves norepinephrine out of the synaptic cleft and into the pre-synaptic nerve terminal. The net result of this effect is to increase the amount of norepinephrine at the post-synaptic receptor, which results in an increased level of central nervous system excitation. In man, this excitation first appears as a cortical stimulation, and the individual becomes garrulous, restless, and excited. In laboratory animals this effect appears as an increase in motor activity, and increased locomotor activity is also seen in the horse. The effect on locomotor activity in the horse is not, however, like anything as marked or as clear-cut as that due to apomorphine or the narcotic analgesics. Thus, although the spontaneous locomotor activity of these animals can be raised far above that of baseline activity, large amounts of the drug are required to produce these effects (Figure 6). In addition, the motor response is characteristically different from

that produced by dopaminergic agonists in that it appears primarily as a restlessness rather than as coordinated, purposeful locomotor activity. This qualitative difference has been loosely described in our laboratory as the difference between a fast run (apomorphine or fentanyl) and a horse attempting to do the foxtrot (cocaine).

It is characteristic of the effects of stimulant drugs in animals that their action is biphasic. At low doses drugs such as cocaine act to stimulate, and a response such as locomotor activity is increased. However, as the dose of the stimulant is increased, the animal becomes overstimulated and loses the ability to coordinate and perform the task in question. Using a highly-sensitive variable-interval responding apparatus in which a horse breaks a light beam for food, we have been able to show that horses are stimulated by doses of cocaine of as low as 4 mg/horse.¹⁵ If the dose was increased, however, the rate of responding declined below control as the animal entered a phase of inhibition. This same effect has also been observed in human athletes, and Harold Conally, the Olympic hammer champion, reports trying amphetamines at one point in his career and then abandoning them when he found that they interfered with his coordination. There is no reason not to suppose that this classic biphasic response to cocaine does not occur with other central stimulant drugs and does not occur on the track. This biphasic response to stimulant drugs and the variability between horses in the dose which produces peak stimulation makes the selection of the correct dose of stimulant drugs for performance work critical.

In the cardiovascular system, low doses of cocaine may depress the heart rate, but higher doses increase it. Blood pressure tends to rise due to the increased heart rate and vasoconstriction. There is no evidence that cocaine increases the intrinsic strength of muscular contraction, and the relief of fatigue from cocaine seems to result from central stimulation, which masks the sensation of fatigue.⁶

Cocaine is markedly pyrogenic and appears to have a direct action on the heat-regulating centers, for the onset of "cocaine fever" in man is heralded by a chill, which indicates that the body is adjusting its temperature to a higher level. The increased muscular activity due to cocaine and vasoconstriction also tends to increase body temperature. Cocaine pyrexia, usually a striking feature of cocaine poisoning, can easily be elicited in animals, and heat stroke would seem to be a particularly likely problem in horses running on cocaine in warm climates.

LOCOMOTOR RESPONSE TO I.V. COCAINE
IN HORSES

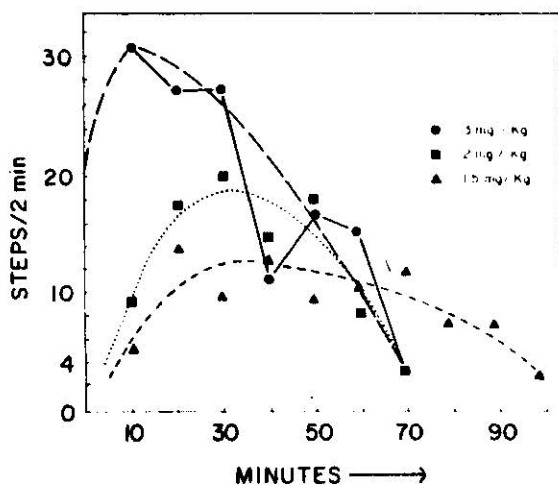


Figure 6. Locomotor response to cocaine in the horse. The symbols show the locomotor response to 1.5 (▲), 2.0 (■) and 3.0 (●) mg/kg of cocaine IV. Locomotor activity was measured as described by Tobin *et al.*¹⁵ and spontaneous activity after a saline injection is about 4 steps/2 minutes.

Cocaine is well absorbed from all sites of application, including mucous membranes.⁷ Cocaine is a local anesthetic in concentrations as low as 0.02%, which block sensory nerve endings, and higher concentrations block conduction in nerve trunks or produce anesthesia on application to mucous membranes or the eye. Cocaine is recommended only for topical anesthesia in veterinary medicine and should not be injected into tissues. Doses as low as 600 mg have been reported to cause toxic effects in the horse. Although cocaine has been reported to be hydrolyzed in the gastrointestinal tract and thus inactive by the oral route, at least 2000 years of leaf-chewing experience by Indians and some recent experimental work has shown that good blood levels of the drug are attained after oral administration.

After IV injection in the horse, cocaine is eliminated with an apparent plasma half-life of about 45 minutes (Figure 7). The period for which cocaine or its metabolites appear in urine is not clear, but preliminary data suggest that very little appears in urine as unchanged cocaine. Blake and co-workers¹ have reported an analytical method for cocaine in which the ecgonine portion of the molecule is split out and a derivative form for electron capture detection. The yields in this reaction procedure are unknown, and it should always be kept in mind that this method only identifies a fragment of the cocaine molecule, which fragment also likely occurs in plant alkaloids other than cocaine.

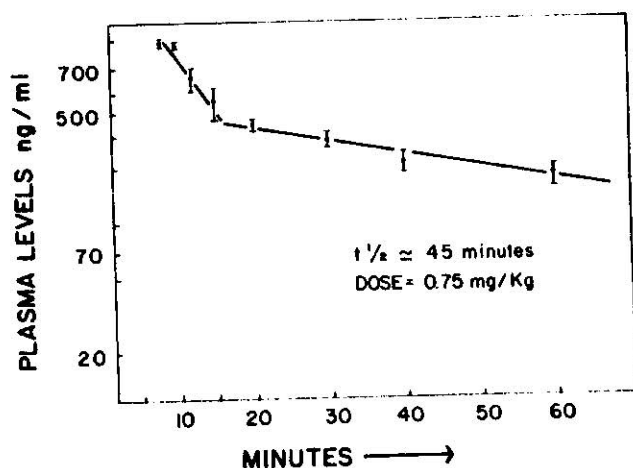


Figure 7. Plasma half-life of cocaine in the horse after its IV injection. The solid circles (●—●) show plasma levels of cocaine after IV administration of 0.75 mg/kg cocaine to four horses.

In conclusion, a number of facts emerge from these¹⁷ reviews and the work in our laboratory on the actions of stimulant drugs in horses. It appears that clear-cut locomotor stimulation, as an unmistakable tendency on the part of the horse to trot or run, is

primarily associated with dopaminergic stimulation. Apomorphine is clearly the most effective drug in this area, but its effects are very erratic. Because of this variable response and the short period for which the horse responds to apomorphine, it would be a most difficult drug to study in performance trials. Of further interest is the fact that though apomorphine has apparently been widely used on the track, to my knowledge no performance trials have been done with it. A final comment might also be that the apparent fear and clear-cut stimulation observed in animals on apomorphine are sufficient reason to ban the use of this drug in racing horses, because it seems a very likely candidate to cause injury to horses and people.

Next to apomorphine, the narcotic analgesics were the most clear-cut locomotor stimulants tested. Fentanyl produced a brief but intense locomotor stimulation, and our horses remained reasonably alert and well-coordinated unless the dose was above 8 mg/1000 lbs. This stimulant action of fentanyl is of particular interest because no signs of depression were seen in any of our experiments with narcotic drugs. Despite this, both the California Rules of Racing and the American Horse Shows Association list fentanyl as a depressant drug, and their basis for this classification remains unclear. Despite the fact that morphine has been known as a stimulant drug in horses for many years, the only studies on the performance effects of narcotics in horses are those of Sanford,¹⁴ who noted that morphine and a combination of etorphine and acepromazine increased speed in performance tests when given in low doses. However, no experimental details or data are available. In other experiments, Gabel⁴ reports that 3 mg of fentanyl administered IV to three Standardbred horses produced no significant improvement in their times to pace one mile. Again, however, these are preliminary results and difficult to evaluate.

The classical central stimulants such as amphetamine, methamphetamine, caffeine, and cocaine do not appear to specifically stimulate locomotor activity in the horse in the same way as apomorphine and the narcotics. Rather, they appear to increase the general level of excitability of the horse and may thus secondarily increase his running ability in the same way as methamphetamine potentiated the motor response to fentanyl.¹⁷ Strangely, these less clear-cut motor stimulants have been much more thoroughly studied in the horse than apomorphine or the narcotics. The general consensus of these studies seems to be that these classical central nervous system stimu-

¹ Immobilon. Reckitt and Coleman, Ltd. Hull, England.

⁴ Gabel, A.: Personal Communication. The Ohio State University, Columbus, OH.

lants can, or are likely to, improve performance in horses. Whether or not the data on which these conclusions are based would withstand rigorous statistical analysis is not clear.

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Abstracts

Papers presented at the AAEP 24th Annual Convention

Feeding on Horse Breeding Farms

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Most inquiries about feeding horses concern young stock and brood mares. We have suspected that many brood mares are poorly fed. Others have associated epiphysitis, splints, and flexure deformities with overfeeding and rapid growth. We have evaluated performance objectives and feeding programs on 12 breeding farms. Two had problems with splints and epiphysitis, and one complained of splints particularly in the progeny of one stallion. The other nine farms had no recognized growth problems despite overfeeding of young horses from six to 18 months of age which ranged from 11 to 183% above daily intakes recommended by The National Research Council. We concluded that overfeeding *per se* is not a sufficient cause of splints, epiphysitis, or flexure deformities, and that the extent to which it may facilitate the expression of any inherited predisposition to these abnormalities remains uncertain. We recommended correct diets (g nutrient/g feed) in regard to the contents of energy, protein, calcium, and phosphorus. We also made sure that the diet contained

adequate iron, manganese and selenium. But we left rations (daily intakes, kg/day/animal) to the discretion of the horseman who should determine the derived rate of growth.

No concentrate was suitable for feeding with alfalfa hay, so we were obliged to formulate concentrates for this purpose. About half of the proprietary concentrates were suitable for use with timothy hay; they contained 14 to 18% protein, 0.6 to 1.1% calcium, and 0.5 to 0.7% phosphorus. The other concentrates contained insufficient phosphorus for any use in horses, except perhaps maintenance. Most farms used the same concentrate for all young stock, including use as creep feed for foals still sucking mares. We recommended mixing this standard concentrate with special products for young herbivores, which contain more protein of high quality.

Only two of 12 farms had exemplary feeding programs for brood mares. Many were feeding no concentrate during late gestation or lactation. We found deficiencies of energy, protein, and phosphorus during gestation, and energy, protein, phosphorus, and especially calcium during lactation. We recommended daily intakes of brood mares, partly for humane reasons and partly because they are less easy for an untrained eye to perceive than the relationship of ration to growth.

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