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

Thomas Tobin, D.V.M., Ph.D.
W.E. Woods, M.Sc.

From the Kentucky Equine Drug Research Program, Department of Veterinary Science, College of Agriculture, University of Kentucky, Lexington, KY 40506.

The central nervous system of the horse is, like our own central nervous system, composed of billions of nerve cells or neurons all intercommunicating in very definite and specific ways. Each gram of cerebral cortical gray matter contains about 200 million neurons, and large neurons in the cerebral cortex may synapse with as many as 3,000 to 4,000 other neurons.[8] These nerve cells are organized into neuronal pools which include structures such as the basal ganglia, the cerebellum, the pons, and the medulla. The primary functions of neurons in these neuronal pools are to transmit, store, and modulate information in the central nervous system (CNS).[7] There are two principal ways in which neurons perform the function of transmitting information.

Figure 1 shows, in greatly simplified form, the basic structure of a neuronal pool. Information enters the pool along the input fibers (solid fibers), which divide, spread over a large area in the pool, and finally synapse with the dendrites or cell bodies of the neurons in the pool. Information coming into the pool passes along the axons of the input cells until it reaches the terminal "synaptic boutons" or synapses, where the axons make contact with another nerve cell. It is at these terminal junctions, called synapses, that the nerve cell transmits its information to another cell.

Nerve cells transmit messages along their length electrically. The electrical activity of nerve cells can be interfered with in a number of ways, and the one most commonly used by veterinarians is local anaesthetics. Local anaesthetics block the electrical conduction (depolarization) mechanism, and in this way prevent the transmission of information. When applied locally, therefore, they produce local anaesthesia. However, if local anaesthetics get into the CNS, they initially have the opposite effect and produce central nervous system stimulation. This anomaly is explained by assuming that local anaesthetics in the brain act on inhibitory pathways, and that suppression of these inhibitory pathways gives rise to the excitement that can be seen after large doses of local anaesthetics.

BASIC ORGANIZATION OF A NEURONAL POOL

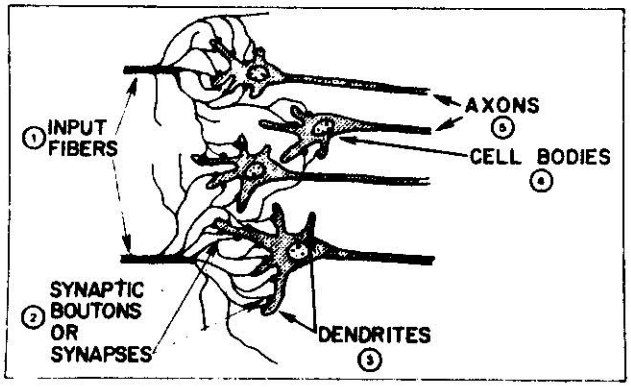

Figure 1. Basic organization of a neuronal pool. Information enters the neuronal pool as an electrical signal traveling down the axons of the input cells (1). These input fibers divide and make contact (2) at synapses (synaptic boutons) with the dendrites (3) of the pool neurons. A chemical signal passes across the synaptic cleft, electrically activates the dendrites, and the signal is transmitted on down the cell bodies (4) and axons (5).

Two other drugs which act on electrical transmission in neurons are the cardiac glycosides and the puffer-fish poison, tetrodotoxin. The cardiac glycosides block the recharging mechanism of the cell membrane (the sodium pump), and tetrodotoxin acts to very specifically block the electrical discharge. However, since both of these drugs act on mechanisms which are fundamental to all nervous tissue, there is little or no subtlety in their action in the brain. Among these three agents, the local anaesthetics are clinically useful only because the veterinarian can place them exactly where he wants with his syringe and needle. For subtle stimulant and depressant effects on the brain, far more selective sites of action are required, and these sites are provided by the synapses of the central nervous system.

In the organization of the brain, the synapse is the structure through which information is transmitted from cell to cell. Electrical transmission is apparently not suited to this task, perhaps because it may be difficult to modulate. For any nervous system which is to function above the level of a "knee-jerk response," subtle modulating mechanisms, which allow messages to be selectively suppressed or amplified, are required. In mammalian brains this suppression or amplification of messages takes place primarily at synapses, and it is here that we find all the sites of subtle drug effects.

The synapse is the specific cellular structure at which information is transmitted between two cells by the release of certain small molecules from one cell and their recognition by the neighboring cell. Since the structure is called a "synapse," the chemical which carries the message is the "synaptic transmitter," or neurotransmitter, or neurohormone. At this point nobody knows how many neurotransmitters there are in the brain, but a list of known or suspected neurotransmitters is presented in Table 1.[a] What makes the neurotransmitters so exciting and useful for the pharmacologist is that particular neurotransmitters are often associated with relatively specific functions in the brain. Thus the neurotransmitter norepinephrine in the brain is broadly associated with mood, and in the human, mood-elevating drugs appear to be associated with increased norepinephrine levels. The neurotransmitter dopamine appears to be associated with motor activity, and dopaminergic drugs such as apomorphine can dramatically increase motor activity in the horse. Finally, and perhaps most clear-cut of all, the endorphins are endogenous opiate neurotransmitters and are associated with pain suppression. This endorphin synaptic system is, of course, the synaptic system which provides receptors for opiate drugs. From these few examples it is clear that many of our useful drugs produce their effects by acting on synapses. Because of the central importance of the synapse in understanding the pharmacology of drugs acting on the CNS, it will be useful for us first to look at the structure of the synapse in some detail.

A synapse morphologically appears as a swelling on the end of a nerve where it makes contact with another nerve (Figure 2). It consists of a presynaptic terminal, which is the tail-end of one nerve, a synaptic cleft, which is a space between the nerves, and a postsynaptic portion, which is the beginning of another

TABLE 1[a]

Known or probable neurotransmitters.

1. Acetylcholine	11. Dopamine
2. γ-Aminobutyric acid	12. Enkephalin
3. Glycine	13. β-Endorphin
4. Gaurine	14. Angiotensin II
5. β-Alanine	15. Oxytocin
6. Glutamic acid	16. Vasopressin
7. Aspartic acid	17. LH-RH
8. Cysteic acid	18. Substance P
9. Homocysteic acid	19. Neurotensin
10. Norepinephrine	20. Somatostatin

[a] From Cooper, Bloom & Roth, 1978.[4]

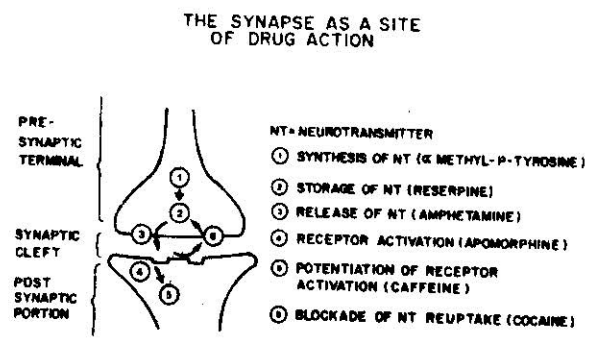

Figure 2. The synapse as a site of drug action. The presynaptic portion of the terminal contains biochemical pathways for the synthesis (1), storage (2) and release (3) of the neurotransmitters. In the adrenergic neuron, synthesis and storage are blocked by α methyl-p-tyrosine and reserpine which, therefore, are both tranquilizers. Release of norepinephrine (3) is stimulated by amphetamine and methylphenidate which are thus stimulant drugs. Apomorphine directly stimulates dopaminergic receptors in the dopaminergic synapse (4) resulting in locomotor stimulation. In the noradrenergic synapse caffeine acts postsynaptically to (5) potentiate receptor activation by norepinephrine, and is thus a stimulant. In the synaptic cleft cocaine (6) acts to prevent presynaptic uptake of norepinephrine, increasing its concentration at the receptor level and thus producing its stimulant effects.

neuron. The presynaptic portion will have the necessary biochemical pathways to synthesize the neurohormone, usually some granular or vesicular mechanism for storing it, and a method for releasing it. Once released, the neurohormone diffuses across the synaptic cleft and activates receptors for the neurotransmitter on the postsynaptic membrane. After the neurotransmitter has activated its postsynaptic receptors, it must be gotten rid of, either by enzymatic hydrolysis, or sometimes by re-uptake into the presynaptic terminal by a specific transport system.

This fairly complex mechanism and the fact that there are a large number of known neurotransmitters obviously allows for an even larger number of possible sites of drug action. Examples of the mechanisms by which some drugs of particular interest to equine practitioners act on the synapse include most of the important stimulants and depressant drugs. Reserpine produces its principal pharmacological action by blocking storage of the neurohormone norepinephrine in the presynaptic storage granules. In the reserpinized animal only about 20% of the normal norepinephrine stores are found in the storage granules, and this depletion of an excitatory neurohormone accounts for the sedation found after reserpine.

Once norepinephrine is released from the presynaptic terminal, its function is to activate the adrenergic receptors on the postsynaptic membrane. Amphetamine, methamphetamine, and methyl-

phenidate* all produce their pharmacological effects by accelerating the release of norepinephrine from the presynaptic terminal. This increased release of norepinephrine produces the excitement seen after amphetamine and methamphetamine. Some drugs, on the other hand, act by directly stimulating the postsynaptic receptors. The best example of a drug which does this is apomorphine, which directly stimulates the postsynaptic receptors for dopamine and produces the locomotor activity so characteristic of apomorphine. The phenothiazine tranquilizers such as acepromazine produce their pharmacological effects by directly blocking postsynaptic adrenergic and dopaminergic receptors and preventing the normal release of neurotransmitters from having any effect.

Another point of action for drugs on the adrenergic synapse is on the mechanism by which the neurohormone is removed from the cleft. As pointed out earlier, norepinephrine is pumped out of the cleft back into the presynaptic terminal. This process is very specifically blocked by cocaine, and cocaine, therefore, gives rise to increased concentrations of norepinephrine on the receptors in the synaptic cleft area and thus gives rise to CNS excitation.

Other central stimulants inhibit the breakdown of norepinephrine by the enzyme monoamine oxidase. Thus monoamine oxidase inhibitors such as phenelzine or tranylcypromine produce a potent and long-lasting inhibition of this enzyme, and thus a sustained elevation of mood and behavior in humans and also, presumably, in horses.

These, then, are some of the mechanisms by which centrally acting drugs produce their pharmacological effects. We will now consider the most important of these drugs individually and detail their actions on the horse. The first we will consider is amphetamine, the classic central nervous system stimulant in both man and the horse.

Amphetamine

Amphetamine has a long history of use in racing, dating from its introduction into human and veterinary medicine prior to world War II. Amphetamine was widely used by the military forces on both sides during World War II, primarily due to the fact that it increases wakefulness and alertness and decreases the sense of fatigue. Prolonged use in humans, however, is always followed by fatigue, depression, and psychosis.

* Ritalin. Ciba Giegy. Ardsley, NJ.

The amphetamines began to appear in postrace equine urines soon after World War II and enjoyed a period of popularity that may still continue in some racing jurisdictions. More recently, however, with the development of sensitive thin layer chromotography and gas chromotography methods for their detection, use has become relatively easy to control and racing jurisdictions no longer have a problem with amphetamine abuse.

The amphetamines produce their effect by stimulating the release of norepinephrine and dopamine from presynaptic storage sites.[4] Thus in animals in which synthesis of these neurotransmitters has been blocked by use of the experimental drug αmethyl-p-tyrosine, amphetamine does not produce its characteristic effects. However, which of these two neurotransmitters is most important for the pharmacological actions of amphetamine is not yet clear.

The amphetamines are among the most potent of the sympathomimetic amines with respect to CNS stimulation. Animals given amphetamine show tremor, restlessness, increased motor activity, agitation, and sleeplessness, effects thought to be due to stimulation of the cerebral cortex. The d-isomer of amphetamine is about 12 times more potent than the l-isomer in producing these effects. In the human, amphetamine increases the duration of performance before fatigue sets in, and the effects of fatigue are reversed, particularly when performance is reduced due to lack of sleep.[19] These actions led to their use by airmen during World War II and account for their use by truck drivers and students cramming for exams.

Methamphetamine is closely related chemically to amphetamine and ephedrine. Small doses of methamphetamine have prominent effects on the brain without significant cardiovascular actions, while larger doses produce marked cardiovascular effects.

We have studied the actions of methamphetamine on spontaneous motor activity in the horse in our laboratory. Unlike the clear-cut motor response which one sees after fentanyl or apomorphine, the locomotor response to methamphetamine alone is small. However, if the animal is injected with small doses of fentanyl and methamphetamine together, the methamphetamine potentiates the fentanyl-induced locomotor response and the response persists for a period after the motor response to fentanyl would normally have decayed (Figure 3). This prolonged motor response after methamphetamine suggests a relatively prolonged course of action for methamphetamine after its intravenous administration.

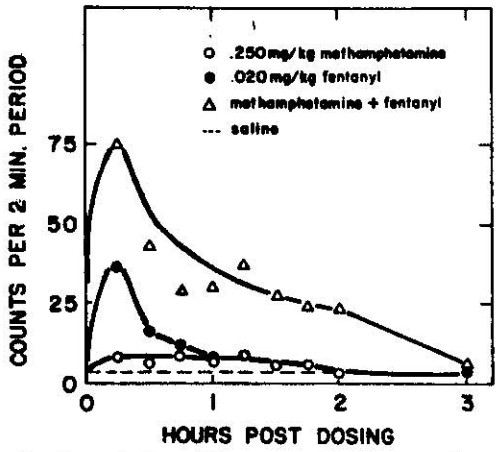

Figure 3. Potentiation of locomotor response to fentanyl by methamphetamine. The open circles (○-○) show the locomotor response of horses after 0.25 mg/kg methamphetamine by rapid IV injection, while the solid circles (●-●) show the response after 0.020 mg/kg fentanyl IV. The triangles (Δ-Δ) show the locomotor response to these drugs administered simultaneously, while the dotted line shows the response to saline alone. All data points are means of experiments on four different horses.

In the circulatory system, the amphetamines generally raise blood pressure and cause a reflex slowing of heart rate, so cardiac output is not increased by therapeutic doses of these drugs. Studying the cardiovascular actions of amphetamine in the horse, Smetzer and co-workers[15] found that amphetamine alone caused a small but significant increase in heart rate and blood pressure. If vagal inhibition was blocked by the use of atropine, amphetamine had much greater effect on heart rate. In the exercised horse these workers found a much greater incidence of ectopic beats and second degree AV block after exercise. Smetzer[15] concluded that in the exercised horse the release of norepinephrine by amphetamine probably caused many of the ectopic beats by increasing the automaticity of subordinate pacemakers. Another action of amphetamines includes the relaxation of bronchial muscle, but this effect is not large enough to be useful. The respiratory center is usually stimulated by amphetamines, and though this effect is small in normal animals, it can be substantial in animals with respiratory depression.

Thereaputic doses of amphetamine cause a modest increase in metabolic rate (10% to 15%) and Gabel[b] and co-workers report a significant increase in body temperature in horses dosed with 250 mg of amphetamine and paced for one mile under racing conditions.

The disposition and metabolism of amphetamine in the horse has been studied in some detail by Baggot and Chapman *et al.*[1-3] Studying the kinetics of amphetamine in Shetland ponies, Baggot[1] injected 0.66 mg/kg intravenously and took his first blood samples at 30 minutes postdosing. The distribution phase was apparently complete within 30 minutes, at which point plasma levels on the order of 200 ng/ml were observed. These had declined to less than 15 ng/ml at six hours postdosing, to give an apparent half-life for this drug in the horse of about 1.4 hours, somewhat faster than an apparent half-life of about two hours seen in later experiments by this same group.[2] Unfortunately, Baggott and co-workers did not report any clinical or behavioral changes in these animals.

In studies on the metabolism of amphetamines in the horse, Chapman and Marcroft[3] found that 84% of C^{14} amphetamine was excreted within 24 hours, of which about 4% was amphetamine. Because amphetamine is extensively metabolized in the horse and only a small portion of the drug is excreted in the urine, its plasma half-life is largely independent of urinary pH.[2] On the other hand, as a basic drug, a much higher proportion of both amphetamine and its basic metabolites are found in acidic urine, which makes the drug easier to detect.[3] The main excretion products are 4-hydroxyamphetamine (free and conjugated), free and conjugated amphetamine, and 1-phenylpropan-2-ol (12%) and 1-phenylpropan-2-one (28%). However, Chapman's results were in contrast with those of Karawya *et al.*[9] who reported that up to 55% of a dose of unlabeled amphetamine was excreted as the parent drug in the urine over 48 hours. Karawya's horses, however, were producing an acidic urine (pH 6.0) in contrast with the alkaline urine (pH 7.8) of the horses of Chapman and Marcroft.[3]

Ray and co-workers[12] have studied the disposition of methamphetamine in the horse and its "clearance times" in plasma and urine. After 150 mg methamphetamine intramuscularly (IM) in six horses, these workers found plasma levels of methamphetamine peaked at about 43 ng/ml within 20 minutes of drug administration and then declined in a complex nonexponential fashion to be no longer detectable in plasma about eight hours after dosing (Figure 4). Salivary levels of methamphetamine were always somewhat less than plasma levels of the drug, as is usual with basic drugs.

Urinary levels of methamphetamine reported by Ray *et al.*[12] were remarkably high after this dose, peaking at 7 μg/ml four hours after dosing and then declining rapidly to about 500 ng/ml at 12 hours after dosing. Thereafter, the decline in urinary levels was relatively slow, and traces of methamphetamine were still

[b] Gabel, A.A.: *personal communication*, The Ohio State University, 1978.

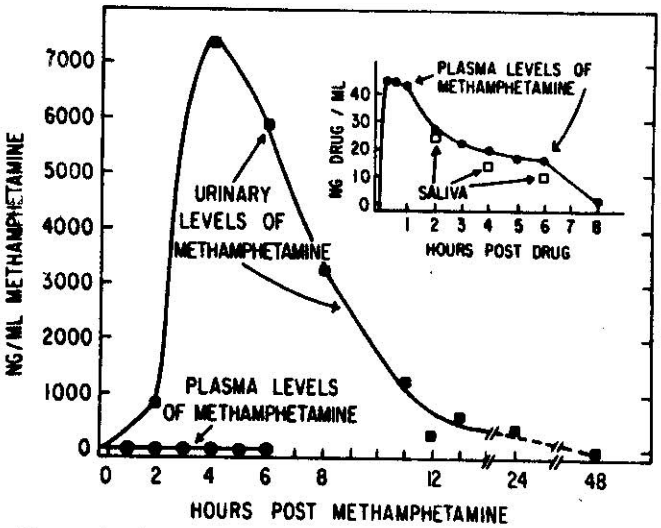

Figure 4. Plasma, saliva, and urinary levels after intramuscular administration of methamphetamine in the horse. Horses were dosed with 150 mg of methamphetamine IM at indicated zero time. The solid squares (■-■) show mean urinary levels of methamphetamine, which ranged up to 200 times the levels observed in plasma (solid circles, ●-●). The inset in the upper right-hand corner shows the relationship between plasma levels of methamphetamine (solid circles, ●-●) and salivary levels of methamphetamine (open squares, □-□) on an increased scale. All data points represent means of experiments on eight different horses and are replotted from Ray *et al.*[12]

detectable in urine at 48 hours after dosing. It seems prudent, therefore, to allow at least 48 hours after dosing with amphetamine or methamphetamine for the urine to clear, particularly in the case of methamphetamine, where massive urinary levels of this drug are observed.

Studying the actions of amphetamines in horses, Stewart[16] dosed three Thoroughbred horses with about 100 mg of amphetamine intravenously (IV) 30 to 60 minutes before exercising them. Prior to exercise he found that amphetamine caused an increase in the respiratory rate but had no significant cardiac effects. He then galloped these horses over distances of between 800 and 1600 meters and found that the gallop speed was improved in each of five trials. The improvement in speed ranged from 0.4% to 8.3%, with a mean improvement of 2.4%, which was not considered statistically significant.

Sanford and co-workers[13,14] studied the effects of methamphetamine on timed circuits at the collected and extended trot, and the canter, using three or four horses in each study. Methamphetamine was given IV at a dose of about 45 mg (0.4 mg/kg) one hour before testing. At this dose methamphetamine was found to increase speed at all paces tested ($P = < 0.02$) without affecting coordination. A dose of about 20 mg increased speed at the trot only. On the gallop test, however, the effect of methamphetamine was variable, with only one horse showing an increase in speed at a dose of 0.2 mg/kg.

Outside of their stimulant action in fatigued or perhaps moribund patients, there are relatively few indications for amphetamine in equine medicine. The amphetamines are potent respiratory stimulants and have been recommended for treatment of anaesthetic respiratory collapse. Recommended doses in the horse are between 100 and 500 mg subcutaneously, and it is suggested that if amphetamine is given in large doses IV that it should be given slowly, as death in the human has followed rapid IV injection of 120 mg. Symptoms of amphetamine toxicity in the horse have not been described, but might be expected to include convulsions, hyperpyrexia, circulatory collapse, coma, and death, with cerebral hemorrhage as the main pathological finding. The phenothiazine tranquilizers effectively control the CNS symptoms, and may also help reduce an elevated blood pressure. Chronic amphetamine intoxication, which causes vivid hallucinations and delusions in the human, is unlikely to be seen in the horse.

Ephedrine

Ephedrine occurs in certain plants of the genus *Ephedra*, a family of small shrubs distributed widely throughout the world. The species of plants containing ephedrine are native to China and Tibet, and the plant has been used in Chinese medicine for over 5,000 years. During the 1930s the plant was grown in the middle west of the United States, but most ephedrine now used is prepared by organic synthesis.

Ephedrine is closely related pharmacologically to the amphetamines. It both stimulates the release of norepinephrine from storage sites and directly stimulates adrenergic receptors. Its central stimulant actions are less than those of amphetamines, but its peripheral effects are more marked.

The actions of ephedrine in horses were studied by Fujii and co-workers,[5] who dosed three Thoroughbred horses with 100, 300 and 500 mg of ephedrine subcutaneously and tested them about one hour after injection. These workers reported a performance-stimulating effect which was apparently less marked and easier to control than that observed after caffeine. They reported that ephedrine induced very frequent second degree AV blocks. Consecutive second degree AV blocks and SA blocks were also observed. Ephedrine also brought about an increase in the respiratory rate during the period of standing be-

fore the exercise, and caused restlessness in some of the horses after exercise. The restlessness was not so serious, however, as to make the horses unmanageable. The authors concluded that ephedrine was inferior to caffeine in improving performance and that its use was likely associated with more risk than caffeine.

Studies in man have shown that the cardiovascular efferts of ephedrine are less marked than those of epinephrine, but that they persist for up to 10 times as long. In man, the force of myocardial contraction is increased by ephedrine, and systolic and diastolic blood pressures are usually raised. Bronchial muscle relaxation also occurs with ephedrine, but the effect is less marked than with epinephrine. Similarly, CNS stimulation after ephedrine in man is less marked than after epinephrine.

In an unpublished study by Chapman and Marcroft (cited by Moss[10]), 87% of the C^{14} in a dose of [14^{c}] ephedrine was excreted in the urine within 24 hours. These workers identified norephedrine, 4-hydroxynorephedrine, and 4-hydroxyephedrine, both free and conjugated, which comprised about 18% of the radioactivity. These metabolic patterns and clearance rates suggest a clearance time for ephedrine of not greater than 44 hours in the horse.

Methylphenidate

Methylphenidate was first introduced into human medicine in 1959, some 15 years after its synthesis and five years after it had been demonstrated to be a central nervous system stimulant. Since then it has been the drug of choice in the treatment of minimal brain dysfunction in children ("hyperkinetic children"). Its spectrum of pharmacological activity is essentially the same as that of amphetamine, but it is considered to have more prominent effects on mental than on motor activity. It is available in tablet or injectable form and it shares the same abuse potential as the amphetamines. Methylphenidate is absorbed well after oral administration and is almost completely metabolized, less than 1% of the parent drug being eliminated unchanged in the urine.

Studying the disposition of methylphenidate in the horse, Tobin *et al.*[18] found an apparent terminal plasma half-life of about 3.4 hours, which corresponded well with the rate of urinary excretion of the drug. After subcutaneous (SC) or intramuscular (IM) injection of the drug, plasma levels peaked at about one hour postdosing (Figure 5) and were no longer detectable after six hours. Urinary levels of the drug peaked between one and three hours postdosing and remained detectable for up to 13 hours postdosing, suggesting that at least 24 hours should be allowed after a dose of methylphenidate for the drug to "clear" the urine. These observations on the pharmacokinetics of methylphenidate in horses are in good agreement with some experiments previously published by Ray *et al.*[12]

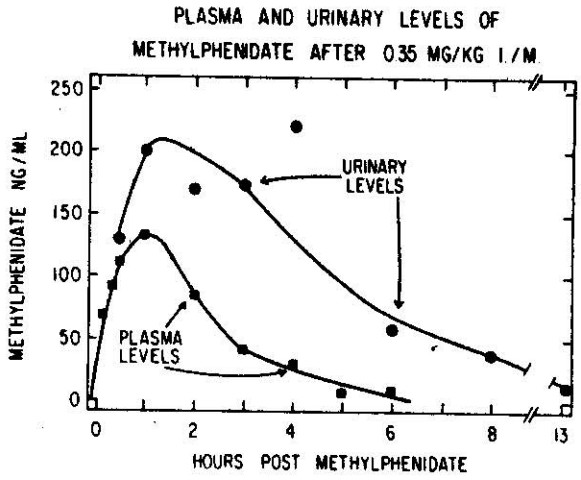

Figure 5. Plasma and urinary levels after intramuscular administration of methylphenidate in the horse. The solid squares (■-■) show plasma levels of methylphenidate and the solid circles (●-●) show urinary levels of methylphenidate after IM administration of 0.35 mg/kg of methylphenidate to four Thoroughbred horses. (Unpublished data, Tobin *et al.*, 1978.)

In our studies with methylphenidate no clear-cut and easily quantifiable behavioral signs of central nervous system excitation were seen. Gabriel and co-workers,[6] however, have reported clinical signs after administration of up to 600 mg of methylphenidate intramuscularly to horses. In these studies, doses of methylphenidate as small as 50 mg doubled the respiratory rate of horses within 15 minutes after dosing. When the dose was increased to 400 mg, the respiratory rate peaked at about 60 movements/minute, and if the dose was further increased the respiratory rate became too rapid to count. No effect on pulse rate was seen until 400 mg was administered, and the pulse rate more than doubled after 600 mg/kg. Along with the increase in pulse rate, signs of central nervous system stimulation were seen, and the horses became quite restless. Gabriel[6] considered the behavior of his horses so affected by large doses of methylphenidate that it would be relatively easy to pick out methylphenidate medicated horses. He did not, however, make clear how he would distinguish a methylphenidate-stimulated horse from a spontaneously nervous horse. This ability of methylphenidate to make a horse "wild eyed and excitable" in a way difficult to distinguish from spontaneous excitement

has apparently led to the occasional use of this drug in show horses, where such behavior may be desirable.

The only reports of effects of methylphenidate on performance in horses are those of Sanford[13,14] who reported that methylphenidate increased speed in doses which had little effect on coordination. It appears that methlphenidate produced this effect in short gallop screening tests, but no details as to magnitude of dose or effect were given. While suggestive of an effect on performance, a more detailed report on these experiments would be useful.

The clinical indications for methylphenidate in the horse are likely to be similar to those of amphetamine, with the difference that methylphenidate appears to allow the animal to concentrate more on a desired behavior. One interesting reported use for methylphenidate in central Kentucky[c] concerns a stallion which had difficulty in serving who was restored to normal performance by 100 mg of injectable methylphenidate IV one hour before his services were required.

[c] Priest, G.: *personal communication*, The Woodford Veterinary Clinic, Versailles, KY.

Part two of this review on CNS stimulants will appear in the March issue of The Journal.

References

1. Baggot, J.D. and Davis, L.E.: A Comparative Study of the Pharmacokinetics of Amphetamine. *Res Vet Sci*, **14**, (1973): 207-215.
2. Baggot, J.D., Davis, L.E., Murdick, P.W., Ray, R.S., and Noonan, J.S.: Certain Aspects of Amphetamine Elimination in the Horse. *Am J Vet Res*, **33**, (1972): 1161-1164.
3. Chapman, D.I. and Marcroft, J.: Studies on the Metabolism of Symphathomimetic Amines: the Metabolism of (±)-[^{14}C] Amphetamine in the Horse. *Xenobiotica*, **3**, (1973): 49-61.
4. Cooper, J.R., Bloom,. F.E., and Roth, R.F.: *The Biochemical Basis of Neuropharmacology*. Oxford University Press, Oxford, (1978).
5. Fujii, Senji; Inada, Shichiro; Yoshida, Shigeru; Kusanagi, Chiyoko; Mima, Kyosuke; and Natsuno, Yoshihiro: Pharmacological Studies on Doping Drugs for Racehorses. III. Ephedrine. *Jap J Vet Sci*, **36**, (1974): 9-18.
6. Gabriel, K.L., Henderson, B., and Smith, W.F.: Studies on the Physiologic Effects of Methylphenidate in Thoroughbred Horses. *Am J Vet Res*, **142**, (1963): 875-877.
7. Guyton, A.C.: *Basic Human Physiology: Normal Function and Mechanisms of Disease*. W.B. Saunders & Co, Philadelphia (1971).
8. Iversen, S.D. and Iversen, L.L.: *Behavioral Pharmacology*. Oxford University Press, New York, (1975).
9. Karawya, M.S., El-Kety, M.A., Wahba, S.K., and Kozman, A.R.: A Note on a Simple Estimation of Amphetamine, Methylamphetamine and Ephedrine in Horse Urine. *J Pharm Pharmac*, **20**, (1968): 650-652.
10. Moss, M.S.: The Metabolism and Urinary and Salivary Excretion of Drugs in the Horse and their Relevance to Detection of Dope. In *Drug Metabolism—from Microbe to Man*. Taylor & Francis, Ltd, London, (1976): 263-280.
11. Oettinger, L. and Majovski, L.V.: Methylphenidate: A Review. *Sou Med J*, **69**, (1976): 161-164.
12. Ray, R.S., Noonan, J.S., Murdick, P.W., and Tharp, V.: Detection of Methylphenidate and Methamphetamine in Equine Body Fluids by Gas Chromatographic Analysis of an Electron Capturing Derivative. *Am J Vet Res*, **33**, (1972): 27-31.
13. Sanford, J.: Drugs and their Effects on Performance in the Horse. *HBLB Conference of Research Workers*, (April 1973): 40-41.
14. Sanford, J.: Medication Affecting the Performance of Racehorses and its Control. *Proc 19th World Vet Cong*, (1971): 382-385.
15. Smetzer, D.L., Senta, T., and Hensel, J.D.: Cardiovascular Effects of Amphetamine in the Horse. *Can J comp Med*, **36**, (1972): 185-194.
16. Stewart, G.A.: Drugs, Performance and Responses to Exercise in the Racehorse. 2. Observations on Amphetamine, Promazine and Thiamine. *Aus Vet J*, **48**, (1972): 544-547.
17. Tobin, T., Combie, J., and Dougherty, J.: The Pharmacology of Narcotic Analgesics in the Horse. III. Characteristics of the Locomotor Effects of Fentanyl and Apomorphine. J Eq Med Surg, *in press*, (1979).
18. Tobin, T., Woods, W.E., and Valentine, R.E.: Pharmacokinetics and Behavioral Effects of Methylphenidate in Thoroughbred Horses. J Eq Med and Surg, submitted for publication (1978).
19. Weiss, B. and Laties, V.G.: Enhancement of Human Performance by Caffeine and the Amphetamines. *Pharm Rev*, **14**, (1962): 1-36.

Publication No. 47 from the Kentucky Equine Drug Research and Testing Programs, Department of Veterinary Science, University of Kentucky, Lexington, KY 40506. Published as Kentucky Agricultural Experiment Station Article No. 78-4-221 with the permission of the Dean and Director, College of Agriculture.