

## Pharmacology Review: The Phenothiazine "Tranquilizers"

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Until the early 1950s the only drugs which were available to calm nervous horses were drugs like chloralhydrate and the barbiturates. While these drugs would calm nervous and fractious animals, it was only at doses which clearly rendered them drowsy and affected their motor ability and coordination.<sup>15</sup> With the introduction of reserpine and the phenothiazine derivatives in the early 1950s, a class of drugs became available which would render animals less reactive to environmental stimuli with minimal effects on their consciousness, motor ability, and coordination.<sup>4,9</sup> Technically, these drugs were found to block conditioned or learned responses, and the term *tranquilizer*<sup>8</sup> was coined for this group of drugs. However, it subsequently developed that the major action and use of this group of drugs was for the treatment of psychoses in humans. They are therefore now known as the antipsychotic or neuroleptic drugs, and the term *tranquilizer* is considered obsolete. This term, however, is still widely and rather loosely used in equine circles to describe any drug which allows a horse to remain conscious and standing but enables a veterinarian to take substantial liberties with it. It is not, however, in this veterinary usage, in any way a precise term.

Perhaps the subtlest use of this rather heterogeneous group of depressant drugs is to "take the edge" off a horse, but this is primarily a horseman's use. What is required in this situation is a drug which will allow a somewhat nervous horse to perform in a relaxed manner in an unusual or challenging environment. Thus, a "washy" horse which gets excited and "runs his race" in the paddock before the actual race might benefit from being "touched" prerace with a tranquilizer (i.e. administered a small dose). The idea is to give the horse a dose which will keep him from being hyperexcitable in the paddock but will allow him to run "up to form" in the actual race. Other times when a small dose of a tranquilizer might help are: for horses which do not take readily to starting gates; for horses which tense up and "ease over jumps" better on a small dose of tranquilizer; and for show horses. All of these uses require very subtle drug effects, and are

outside of the classical uses of "tranquilizers" as drugs. An additional subtle use of tranquilizers is, of course, in the "nobbling" or stopping of horses, where a slightly larger dose is used, and the objective is to reduce the speed of the horse to the point at which it must lose the race.

A somewhat more substantial tranquilizing effect is required for transport of an animal. The goal here is to reduce the amount of stress experienced by the horse and thus the likelihood of injury or of the horse being stressed to the point where he leaves himself open to a shipping pneumonia. Also, one would hope with judicious medication to avoid the possibility of uncontrollable excitation, with the unwelcome outcome, in air transport, of having to destroy a valuable horse in mid-flight.

The third and perhaps the widest usage for this group of drugs is restraint in a clinical situation. Here, the veterinarian wishes to perform some minor interference on an animal and is interested in safety and control of a conscious standing animal rather than a subtle drug effect.<sup>10,14</sup> However, because animals are easily aroused from, for example, phenothiazine-induced tranquilization, these drugs alone are not the most satisfactory drugs for this rather specialized type of chemical control or restraint.<sup>2</sup> There are now a number of useful drugs or drug combinations available which appear to be fundamentally quite different from and more effective than the classical tranquilizers, and these will be dealt with another time in some detail.

Reserpine, a plant alkaloid, was the first of the classical tranquilizers to be reported on, and Yonkman coined the term *tranquilizer* to characterize the psychic effects of reserpine on humans.<sup>8</sup> At about the same time, a group of French workers synthesized chlorpromazine, the prototype member of the phenothiazine group of tranquilizers. This group has since been expanded to include a very large number of tranquilizers based on the phenothiazine nucleus, only a few of which are used in veterinary medicine. Another family of tranquilizers, called the butyrophenones,<sup>3</sup> has also been developed which, though chemically distinct from the phenothiazines, is pharmacologically quite closely related.

Other drugs which are usually grouped with these tranquilizing agents are the so-called minor tranquilizers, diazepam<sup>a</sup> and chlordiazepoxide hydrochloride,<sup>3b</sup> whose mode of action is quite distinct from reserpine or the

<sup>a</sup> Valium. Roche Laboratories, Nutley, NJ.

<sup>b</sup> Librium. Roche Laboratories, Nutley, NJ.

phenothiazines. A relatively recent introduction to veterinary medicine is xylazine,<sup>c</sup> which is a very potent though relatively short-acting depressant. Lastly, there are a number of other drugs, such as the corticosteroids and thiamine, which are believed to produce tranquilizing effects at certain doses and which are used for this effect under some circumstances.

**The Phenothiazine Tranquilizers.** The prototype of the phenothiazine tranquilizers is chlorpromazine, which is chemically related to the anthelmintic phenothiazine. It was first synthesized in France in 1950 and its pharmacological effects investigated. Like all the phenothiazine tranquilizers, chlorpromazine has a very large number of pharmacological actions, and this property was reflected in one of the first trade names for this drug, *Largactil*. Chlorpromazine, however, is not widely used in equine practice, because it reportedly produces undesirable side effects in many cases.<sup>3</sup> According to Booth,<sup>3</sup> after a few minutes of initial sedation following administration of the drug, the animal may become unsteady, sink backward on its hocks and lunge forward in an uncoordinated manner. The horse may stumble and fall, but then stand up with continued lunging and rearing. This violent reaction reportedly alternates with periods of sedation, from which the horse may return to the uncoordinated excitement state.

Acepromazine (acetylpromazine), an acetylated derivative of promazine, is one of the most commonly used phenothiazine tranquilizers in equine medicine. It is recommended for use in horses at doses of between 0.05 and 0.1 mg/kg (2 to 4 mg/100 lb) for a spectrum of effects which covers the area popularly referred to as "tranquilization" in horses. All the phenothiazine derivatives, including acepromazine, appear to produce at least part of their central effects by blocking dopaminergic receptors in the brain. Dopaminergic receptors are the receptors on which apomorphine and the narcotic analgesics act to produce the trotting response which we detailed previously.<sup>17</sup> Therefore, it would seem reasonable that if the phenothiazines block these receptors they should also act to block the narcotic-induced trotting response, and this indeed turns out to be the case. If one pretreats horses with acepromazine, the trotting response to fentanyl is reduced, and one can use this data to develop both dose-response and time-response data on the pharmacological response to acepromazine in the horse. As shown in Figure 1, after 0.1 mg/kg of acepromazine intravenously (IV), the trotting response to fentanyl is more than 60% inhibited within about 30 minutes

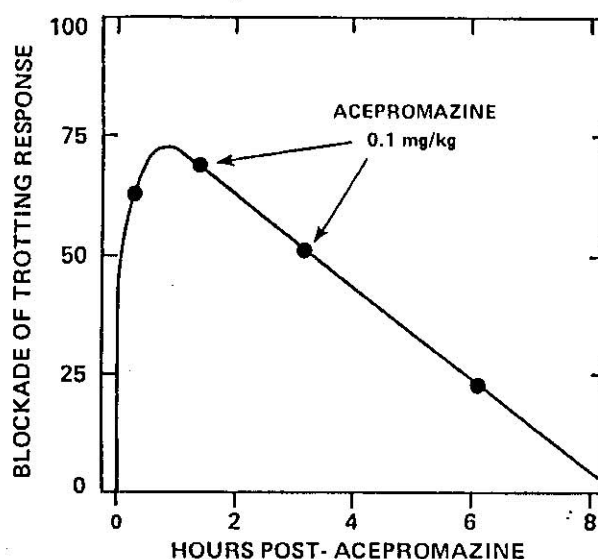


Figure 1. Effect of acepromazine on trotting response to fentanyl. Horses were pretreated with 0.1 mg/kg of acepromazine IV and challenged at the indicated times with 0.02 mg/kg fentanyl. The solid circles (●—●) show percentage inhibition of the normal locomotor response to fentanyl observed in these horses.

after dosing, but the inhibition declines thereafter to disappear by about the eighth hour postdosing. The data provide good evidence for occupation of dopaminergic receptors by acepromazine in the horse and show that the blockade lasts for about eight hours after a 0.1 mg/kg dose. If the dose of acepromazine is reduced, both the extent and time course of the response are reduced, although the time of peak effect remains approximately the same.

In other work, MacKenzie and Snow<sup>11</sup> used 0.5 mg/kg of acepromazine, about five times the dose used in the experiment of Figure 1, as a chemical restraining agent when performing muscle biopsies in seven horses. At these doses, MacKenzie and Snow considered that the tranquilizing effects of acepromazine lasted for 24 hours, considerably longer than the eight-hour response seen at the manufacturer's recommended dose.

Along with a reduction in spontaneous locomotor activity, the phenothiazine tranquilizers markedly reduce respiratory rate, both in the standing horse<sup>13</sup> and even after strenuous exercise.<sup>5</sup> Figure 2 shows the effects of increasing doses of acepromazine IV on the respiratory rate of horses in our laboratory. The mean respiratory rate in control horses was about 17 respirations/minute, which remained constant over the two-hour control period. The smallest dose tested, 0.01 mg/kg, had little effect on the respiratory rate and presumably is a subthreshold dose for a pharmacological response. The next dose tested, 0.04 mg/kg

<sup>c</sup> Rompan Injectable. Haver-Lockhart Laboratories, Shawnee, KS.

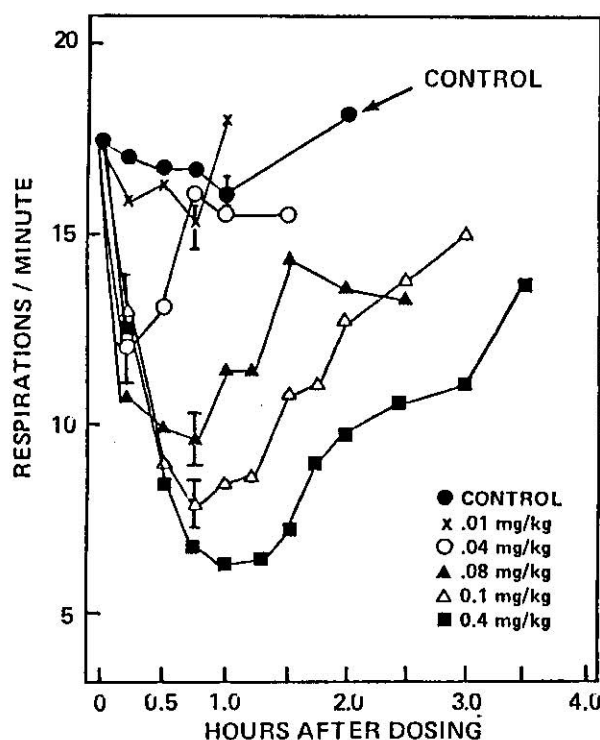


Figure 2. Effect of acepromazine IV on respiratory rate in the horse. The solid circles (●—●) show the respiratory rate in control horses, while other symbols show the respiratory rates observed in these horses after the indicated doses of acepromazine IV. All data points are the means of determinations on four horses, and the vertical bars represent standard errors of the means.

(about 20 mg to a 1000-lb horse), produced a modest respiratory depression peaking at about 15 minutes and returning to control within one hour of dosing. This response presumably parallels the tranquilizing response to this dose of acepromazine IV. If the dose of acepromazine was increased, the depression in respiratory rate observed became more profound and took longer to develop. Thus, after 0.08 mg/kg, respiratory depression peaked at around 30 minutes post-dosing and then returned toward control. After 0.1 mg/kg, the higher end of the manufacturer's recommended dose, the effect peaked after 45 minutes and then slowly declined, not having returned to control by three hours postdosing. At the highest dose tested, 0.4 mg/kg, respiratory depression took one hour to peak and then declined even more slowly, the respiratory rate being still markedly depressed three hours after dosing.

The family of dose-response curves presented in Figure 2 allows for some conclusions of interest to the practitioner. If, as is usually the case, the practitioner wants to work on the horse for about 10 minutes at say 15 minutes after dosing, there is not much point in

giving more than 0.5 mg/kg. This is because tranquilization will apparently be maximal for this time period at this dose. You can produce more "tranquilization" with a higher dose, but you also have to wait longer to allow the effect to develop. Therefore, increasing the dose of a phenothiazine tranquilizer does not appear to accelerate the onset of tranquilization, but just means that with time the effect becomes more profound.

Muir and co-workers<sup>13</sup> have studied the effects of acepromazine on ventilatory variables in the horse in some detail. It turns out that although acepromazine depresses the respiratory rate as breaths per minute, the volume of air respired increases to compensate and maintain ventilation at approximately the same level. Such a depression of respiratory rate is not particularly surprising in standing horses, because it turns out that essentially the same effect is seen in phenothiazine-treated horses after strenuous exercise. This effect was demonstrated clearly by Carey and Sanford,<sup>4</sup> who showed that pretreatment with small doses of acepromazine (0.02 to 0.08 mg/kg) inhibited the exercise-induced increase in respiratory rate up to 50%. Similar results have also been observed by Fujii<sup>6</sup> with chlorpromazine, by Steward<sup>16</sup> with promazine and by Courtot<sup>5</sup> with acepromazine.

Another very obvious and consistent indication of the action of phenothiazine tranquilizers is extension of the penis in stallions and geldings. Figure 3 shows the time course of penile extension in four geldings after dosing with 0.04 and 0.1 mg/kg acepromazine IV. Penile extension was essentially complete within 30 minutes after dosing and at the higher dose remained maximally extended up to about 100 minutes after dosing. However, beyond two hours after dosing the penis was rapidly withdrawn into the sheath, and by the third hour after dosing at this level penile extension had essentially returned to control values. As suggested by this data and the work of Fujii and co-workers<sup>6</sup> who detailed the clinical signs of chlorpromazine administration in horses, penile extension appears to be a relatively sensitive indicator of the action of these drugs.

Extremely rarely following acepromazine, but apparently more commonly with propiopromazine, a long-lasting paralysis of the retractor penis muscle has been observed.<sup>3</sup> This phenomenon is apparently dose related, and is thought to be more common in stallions than in geldings. With propiopromazine, erectile penile paralysis has been observed for up to 18 months after dosing, and even after castration the penis failed to retract completely two years later.<sup>3</sup>

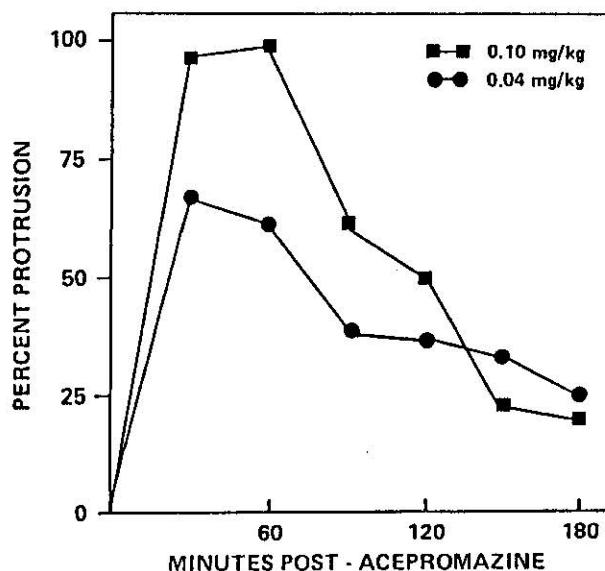


Figure 3. Effect of acepromazine on penile protrusion. Four horses were dosed with the indicated doses of acepromazine, and the time course of penile extension followed. Penile protrusion is plotted as a percentage of the maximal extension observed following 0.1 mg/kg of acepromazine IV.

Other clinical signs of phenothiazine tranquilization were detailed by Fujii and co-workers.<sup>6</sup> These investigators reported ptosis of the eyelids, penile protrusion and postural sway as the most sensitive signs of chlorpromazine administration in horses, appearing after doses of 0.25 mg/kg. As they increased the dose to 0.5 mg/kg, drowsiness, dulling of responses to external stimuli and restlessness became apparent, and the restlessness increased when the dose was increased to 1.0 mg/kg. A decrease in tail tension never became apparent, and it seems reasonable to assume that essentially the same sequence of signs holds for all the phenothiazine derivatives. Additional clinical signs of phenothiazine action include drooping of the head and, at high doses, sweating is commonly seen.

The increasing restlessness reported by Fujii *et al.*<sup>6</sup> is of interest, because a number of workers have reported excitement in the horse after high doses of tranquilizers. Thus, Carey and Sanford<sup>4</sup> report that after a few minutes of initial quiet following the injection of tranquilizers, the horse may become unsteady, sink back and plunge forward in an uncoordinated manner. They report that the horse may stumble, fall and get up, and that bouts of sedation may alternate with bouts of excitement. In a somewhat similar vein, MacKenzie and Snow<sup>11</sup> observed a violent hyperexcitability reaction in a horse after 0.5 mg/kg of acepromazine intramuscularly (IM). This reaction was accompanied by sweating, trembling and restlessness, which lasted about 40 minutes. The cause of these

reactions is not known, although both a sudden drop in blood pressure and a fear response to drug-induced muscular weakness have been suggested as probable causes. However, the work of Hall *et al.*,<sup>4</sup> who measured blood pressure during this response in a Welsh pony, suggests that a drop in blood pressure is not a likely cause.

This response is of particular interest in light of a response observed in our laboratory after administering 0.4 mg/kg of acepromazine by rapid IV injection. Studying the effects of large doses of acepromazine on heart and respiratory rates, we were surprised to find a marked though transient locomotor response in four of five horses which peaked at about 60 steps/2 minutes about 5 minutes after IV injection. Qualitatively, this response did not resemble the lenthyl- and apomorphine-stimulated trotting but rather suggested the animal was falling forward and moved forward just to keep his feet under him. This response is being further investigated but was initially a most surprising response from a dopaminergic blocker.

Another clear-cut central group of actions of the phenothiazine tranquilizers are in the hypothalamic or brain stem areas. This area controls body temperature, respiratory rate and the releasing factors for the pituitary hormones, all of which are affected to varying degrees by the phenothiazine tranquilizers.

The hypothalamic mechanism controlling body temperature is affected in such a way by the phenothiazines that the body temperature of the horse tends to approach environmental temperature. Thus, under normal conditions horses on the phenothiazines become hypothermic, but if ambient temperature is higher than body temperature they can become hyperthermic. However, the usual pattern of response is a degree or two of hypothermia, elevating during exercise, but still remaining a degree or two below the body temperature of untreated controls.<sup>8</sup>

In humans and laboratory animals, high doses of the phenothiazine tranquilizers produce marked effects on the release of hypothalamic hormones. They can block follicle-stimulating and luteinizing hormone release and thus suppress ovulation, the estrous cycle and cause infertility and pseudopregnancy.<sup>8</sup> These effects, however, do not appear to be a serious problem with single doses, and tranquilizers are often used to facilitate the breeding of mares, apparently without any substantial effects on their conception rates.

As well as blocking dopaminergic receptors and thus motor responses, the phenothiazine tranquilizers



also have potent blocking effects on adrenergic and cholinergic receptors. Blockade of alpha adrenergic receptors in the vascular system leads to a drop in blood pressure apparently from about 75 mmHg in control animals to about 50 mmHg within 10 minutes after IM injection of 0.1 mg/kg acepromazine.<sup>2</sup> Associated with this drop in blood pressure, heart rate increased from about 45 beats/minute to about 60/minute. Broadly similar responses have also been demonstrated with promazine by Gabel and co-workers.<sup>7</sup> These are well-known effects of the phenothiazine tranquilizers and lead to their contraindication in shock, where they are likely to exacerbate the circulation defect.

Phenothiazine tranquilizers such as acepromazine are also useful in cases of mild colic, where they appear to relax the G.I.T. and aid in the expulsion of flatus. The basis for this pharmacological effect is not known, but it is likely associated with the cholinergic blocking activity of the drug. In any event, acepromazine has been recommended for use in mild colics,<sup>3</sup> although it should be kept in mind that it must be used with caution in colics that are likely to develop a component of shock.

The effects of the phenothiazines on performance are likely to be among the most subtle effects of this group of drugs, and a number of workers have investigated this aspect of their pharmacology. Thus, Fujii and his co-workers<sup>6</sup> studied the actions of chlorpromazine on Thoroughbred horses at doses of 0.25, 0.5 and 1.0 mg/kg. They found that at these doses chlorpromazine showed pronounced performance decreasing effects, and the horse administered 1.0 mg/kg could not change his pace from a trot to a canter but continued to run at a canter. Like acepromazine, chlorpromazine increased the heart rate, and horses ran with the penis protruded. Chlorpromazine also decreased the respiratory rate, which was evident immediately after exercise. Fujii and co-workers<sup>6</sup> interpreted their results to mean that medication with chlorpromazine, even at very small doses, was likely to interfere with the performance of the horse.

In Australia, Stewart<sup>10</sup> investigated the effects of 0.2 mg/kg promazine hydrochloride on three racehorses in gallop tests. At these doses the horses were clinically tranquilized, and had a sleepy, lethargic appearance, lowering of the head and neck, protrusion of the penis and slight dragging of the hind legs when walking. Small decreases in heart rate were reported after injection of promazine, but the usual marked increase in heart rate occurred when the horses were walked onto the track prior to work.

In 10 gallop tests at this dose of promazine, the horse's speed was decreased between zero and 15%, with a mean decrease of 4%. There was little affect of promazine on heart rate at any time throughout these tests, but respiratory rate was markedly reduced, both pregalloping and immediately after the galloping test. The decrease in speed produced by promazine was statistically significant and clearly shows that promazine at these doses will interfere with racing performance. However, from the clinical signs shown by these animals, it does not appear likely that either Stewart's or Fujii's horses would have passed a prerace examination.

Sanford and co-workers<sup>12</sup> carried out some rather elaborate but preliminary studies on the actions of promazine and acepromazine on speed and coordination in horses. In these trials, horses were injected IM with promazine or acepromazine and then held one hour to allow the drug to act. After this one-hour period, respiratory rate, pulse rate and rectal temperature were measured before saddling the horse. The horse was then ridden 1500 meters to the paddock and taken four times at the walk and four times at the trot over 6 cavaletti, a process which took about 30 minutes. The cavaletti were about 12 inches high and 12 feet apart, and a fault was scored if the crossbar was knocked, yielding a total possible fault score of 192. After the cavaletti (coordination) test, the physiological parameters were again recorded and the horse circled around the paddock, twice at the trot on the right rein, twice at the trot on the left rein, and then twice cantered the same distance on both reins. The horse was then galloped 220 meters and the physiological parameters were again measured. The horse was returned the 1500 meters to the barn, was unsaddled and the parameters again measured. The total distance covered by the horse in these tests amounted to about 4620 meters.

Sanford found that in general the control values on the cavaletti test were quite resistant to changes in ground condition, weather and other variables which horsemen might tend to blame for erratic performance. One horse, Shane, had a mean number of errors on the cavaletti of about 11 faults which was increased to 17 by doses of from 0.04 to 0.06 mg/kg of acepromazine, and more than doubled by 0.08 mg/kg. The canter test was found to be very insensitive to drug effects, and all the other tests were found to be approximately similarly sensitive to drugs. For one horse on the gallop, Sanford noted control times for the 200-meter gallop of about 19.5 seconds  $\pm$  2.4 seconds, which was increased by promazine to about 22.5 seconds after 0.4 and 0.6 mg/kg, and to about 27.5 seconds after 0.8 mg/kg. While these are very

interesting and suggestive results, the small number of horses used in these studies makes it difficult to draw specific conclusions.

The changes in physiological parameters found by Sanford were in good agreement with the known pharmacology of the phenothiazines. Thus, acepromazine was found to reduce rectal temperature in one horse tested by about 1 degree, and body temperature tended to increase with exercise as in the control horse. Pulse rate was little affected after acepromazine, but the respiratory rate was markedly reduced, peaking at about 25 respirations/minute after the gallop test in control horses, but at only about half of this level after treatment with acepromazine.

In other studies, Aitken and Sanford<sup>1</sup> measured heart rates in horses in an attempt to quantitate the effects of these drugs on fear and excitement. In these experiments heart rates were recorded by radiotelemetry from unrestrained horses in box stalls. The horses were challenged with stimuli such as presenting with a whip, opening an umbrella, bursting a balloon and sounding a horn, to which unmedicated horses responded with an increase in heart rate. The drugs studied were acepromazine, azaperone and xylazine. Acepromazine was used at the very substantial dose of 0.2 mg/kg, while azaperone was investigated at 0.4 and 0.8 mg/kg, and xylazine at 2.0 and 3.0 mg/kg. Of seven horses screened for cardiac response in this testing system, four of the most nervous Thoroughbreds were selected for testing.

In general, Aitken and Sanford found that at the doses used, xylazine was the most effective drug, essentially completely eliminating or abolishing the cardiac response to visual stimuli. Azaperone reduced the response, but of the three drugs at the doses tested, acepromazine was clearly the least effective. Furthermore, these workers reported that xylazine was the most consistently effective drug with an absence of undesirable side effects in all horses tested.

Urinary clearance times have long been a problem with the phenothiazine tranquilizers and are likely to remain so for some time. To this author's knowledge, no studies on the plasma half-life of acepromazine in the horse have been reported, and to judge from the transient pharmacological effects of this drug in the horse, its effective plasma half-life must be short. Similarly, there are no published data on the urinary clearance times of phenothiazine tranquilizers or their metabolites using modern testing technology. Using ultraviolet analysis and colorimetric methods, Weir

and Sanford<sup>18</sup> studied the urinary clearance of promazine, chlorpromazine and acepromazine. These studies showed that after the very large dose of 1 mg/kg acepromazine less than 5% of the dose was recovered in the urine. Metabolites of acepromazine could no longer be detected in the urine 32 hours after IM injection and 40 hours after oral dosing. Similarly, after a 10 mg/kg dose of promazine about 10% of the dose administered was eliminated in the urine, the bulk as glucuronide metabolites and small amounts as sulfates and unconjugated drug. After this dose of promazine, metabolites were detected in urine for up to 72 hours in one experiment.

After administration of chlorpromazine (25 mg/kg) up to 20% of the dose administered was detected in the urine, and metabolites were detectable in urine for up to 96 hours. However, in assessing this data, one must keep in mind that the gas chromatographic analytical techniques currently in use in many jurisdictions are likely to be much more sensitive than the techniques used by Weir and Sanford, and the appearance of traces of phenothiazine tranquilizers in the urine for long periods after administration of the last dose has been reported.<sup>8</sup>

In conclusion, the phenothiazine tranquilizers clearly block a wide range of central effects, including locomotor and respiratory responses and control of body temperature. Their central effects are marked, and at clinically used doses they substantially depress alertness and responsiveness in horses and make them easier to handle. There are, however, three characteristics of the pharmacology of the phenothiazine tranquilizers which the equine veterinarian would do well to bear in mind when he uses these drugs. The first is that horses are easily aroused from their depressed or tranquilized state. This was perhaps most clearly shown by Stewart's horses<sup>16</sup> which, though clinically "tranquilized," still showed the anticipatory rise in heart rate when led on to the racetrack. The second is that tranquilizers block conditioned (learned) responses. What this means to the practicing veterinarian is that the horse will not be afraid when you enter the stall to work on him (a learned response), but when you tweak that sore spot you are going to work on he will arouse readily (typical of the phenothiazines) and may kick your head off (an unconditioned or innate response). The third and last point to remember is that nobody has yet published good clearance data for the phenothiazine tranquilizers in urine, so when you give that tranquilizer shot to help loading, transport or minor surgery, it is prudent to ensure that the horse is not likely to be urine tested for at least the next four days.

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