TRANQUILIZERS, ANALGESICS AND LOCAL ANAESTHETICS

T. TOBIN

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BACKGROUND

The major tranquilizers used in equine medicine include the phenothiazine tranquilizers, xylazine and, more recently, the closely related detomidine, and reserpine. Among these agents the phenothiazines and xylazine are relatively short acting. Reserpine, on the other hand, is a long acting agent and its actions can be apparent for days to weeks after administration of the drug.

THE PHENOTHIAZINE TRANQUILIZERS

In North America the most commonly used agent among the phenothiazine tranquilizers is acepromazine. Other agents which have been used in horses include promazine and propiopromazine. Promazine is, however, much less potent than acepromazine and, as such, is likely to be detected in blood or urine testing more readily than acepromazine. Propiopromazine has also been used in horses, but has an unfortunate tendency to produce prolonged extension of the penis, and for this reason is little used in racing horses. In general in North America, acepromazine is the most commonly used tranquilizer in racing horses and, because of its multiple uses, it is in some ways part and parcel of modern horsemanship. Acepromazine is used in breaking and training horses, in loading and transporting of horses, and in the handling of difficult horses by both horsemen and veterinarians. Additionally, acepromazine has long been used in nervous competition horses to regulate or rate their performance and has been used for this purpose in both racing and show horses (Tobin 1981).

Acepromazine and the other phenothiazine tranquilizers have broadly the same pharmacological actions in the horse. At least part of their central blocking actions is due to their blockade of dopamine receptors in the brain. Because of the very clearcut actions of narcotic analgesics to stimulate locomotor activity via the dopaminergic receptors, one can readily demonstrate the blockade of dopaminergic receptors by those drugs. As shown in Figure 1, acepromazine blocks the locomotor response to fentanyl in the horse with the effect peaking at about 1.5 hours after drug administration and then declining to base line at about six hours after dosing (Tobin 1981).

As well as affecting dopaminergic receptors, acepromazine also affects other receptor types, particularly adrenergic receptors. Classically, phenothiazine tranquilizers

affect both alpha and beta adrenergic receptors and in the horse this shows up as a very sensitive effect of acepromazine on haematocrit (Ballard *et al* 1982). The haematocrit in the horse is well known to be sensitive to adrenaline or excitement, each acting to rapidly and substantially increase the haematocrit. What is less well known is that the phenothiazine tranquilizers, particularly acepromazine, act to reduce the haematocrit. While this effect is much less dramatic than the increases seen after excitement, they are nevertheless quite clearcut and are seen after very small doses of acepromazine. In fact, in our hands these were by far the most sensitive responses to acepromazine, being half-maximal at dose levels of as little as 1 mg/horse. This is by far the most sensitive response to acepromazine described in the horse and suggests that very small doses of this drug can have pharmacological effects in the horse.

The next most sensitive response to acepromazine is its effect on penile protrusion in the male horse (Figure 2). This effect is well known and begins to appear after doses of acepromazine in the order of about 4 mg/horse (Ballard *et al* 1982). After intravenous administration of this dose, prolapse of the penis occurred rapidly, reaching its peak response at about 15 minutes after drug administration and returning to near control values by about two hours after administration of the drug. Increasing the dose increased the extent and duration of the response, with the maximal response being obtained after administration of about 160 mg/horse (0.4 mg/kg). This penile protrusion response is a consistent response to phenothiazine tranquilizers, is a relatively sensitive response, and,

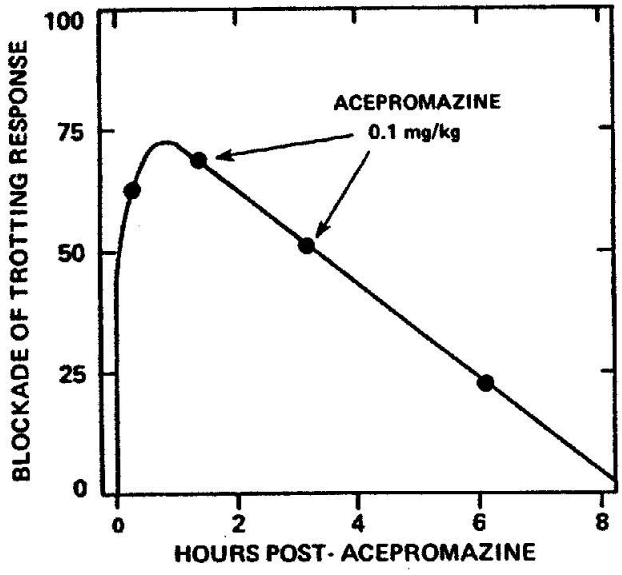

Figure 1:

Time course of the acepromazine blockade of fentanyl-induced trotting. The peak effects of acepromazine on fentanyl-induced trotting are plotted as blockade of trotting against time. The curve and solid circles thus show the time course of action of acepromazine in these horses. Reproduced with permission from *J. Equine Med. Surg.*

for at least one phenothiazine tranquilizer, led to its withdrawal from the market because it was poorly reversible.

Somewhat less sensitive than penile protrusion are two well characterized responses to the phenothiazine tranquilizers: a variable interval responding response and their effects on respiration. The effects of phenothiazine tranquilizers on respiration consist primarily of effects on rate, with the respiratory rate becoming slower, but each respiratory movement deeper, resulting in little overall change in minute volume (Muir and Hamlin 1975). These effects are easily quantified and have been used in our laboratory to characterize the onset of the pharmacological responses to acepromazine. Using this approach we showed that the times to peak onset of the pharmacological effects of acepromazine are dose dependent, taking increasingly larger doses of acepromazine. Similarly, however, we showed that the pharmacological effects of these doses were relatively shortlived, and were not likely to last for more than four hours, at least when estimated from the duration of the respiratory effects.

When we used variable interval responding in an attempt to quantify the central effects of acepromazine, we were surprised to find that we needed to administer relatively

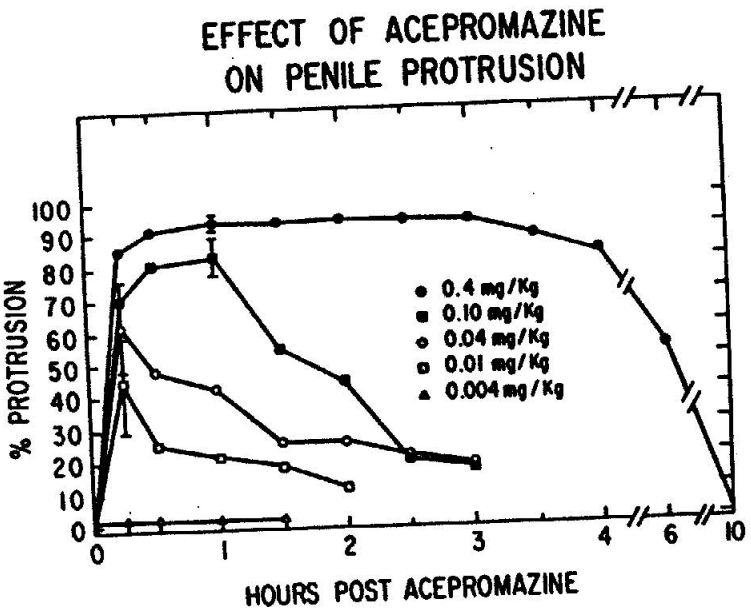

Figure 2:
Effect of acepromazine on penile protrusion in geldings. Acepromazine at 0.4 mg/kg was administered intravenously to four geldings and the maximal length of penile protrusion measured. The symbols show the penile protrusion measured after each subsequent dose of acepromazine, expressed as a percentage of the maximal protrusion seen in each horse (Tobin 1981). (●) 0.4 mg/kg; (■) 0.10 mg/kg; (○) 0.04 mg/kg; (□) 0.01 mg/kg; (△) 0.004 mg/kg.

large doses of acepromazine to produce clearcut effects (Ballard *et al* 1982). Doses of about 4 to 5 mg/horse, which produce marked effects on haematocrit and penile protrusion, had very little effect on the variable interval responding rate, and doses of ten times this amount were required for clearcut effects on the responding rate in these horses. For a drug whose primary action is suggested to be on the central nervous system, this was a surprising finding, but review of the data in the dose response curves suggests that the locomotor response, the central nervous system response and the respiratory effects of acepromazine are all approximately similar and require doses of this drug in the order of 5 to 20 mg/horse for clearcut effects.

In summary, therefore, acepromazine is a potent drug in that doses of 1 mg or less per horse produce clearcut, if subtle, pharmacological effects. Clinically useful effects of this drug require doses in the order of 5-20 mg/horse. While readily detectable in urine, these doses of acepromazine were difficult to detect in blood, particularly with the analytical methods available in the early eighties.

When I started work on acepromazine about eight years ago the analytical techniques available were not very sensitive. Our initial attempts to detect this drug in blood after clinical doses met with little success and we had to increase the dose of drug to about 0.3 mg/kg or about 150 mg/horse to enable us to detect this drug (Ballard *et al* 1982). However, even with the limitations of the technology then available to us, we were able to show that acepromazine, although highly protein bound, rapidly clears the blood and that its volume of distribution in the horse is very high indeed. The upshot of this is that the drug has very low free plasma concentrations, and is generally undetectable in blood after administration of clinical doses of this drug.

More recently we have developed an immunoassay for this drug and used these assays to detect acepromazine in both pre-race blood and in urine of horses post-race (Kwiatkowski *et al* 1988). To detect acepromazine in blood these tests have to be very sensitive indeed since the doses of drug administered are likely to be in the order of about 3 mg/horse or less, and such small doses are challenging to find in blood, and similarly in urine.

However, when we introduced a particle concentration fluorescence immunoassay pre-race test for acepromazine into pre-race testing in Illinois, this test immediately detected the use of this drug pre-race and similarly our enzyme linked immunoassay (ELISA) tests were able to detect the use of these drugs post-race. Gas chromatography-mass spectrometry (GC/MS) confirmation of these immunoassay findings followed, albeit more slowly, and demonstrated the technical practicality of this approach to both pre- and post-race testing.

These immunoassay tests are very sensitive, and readily allow the detection of this drug in blood, and also in urine. Whereas previous doses of this agent in the order of 3 mg/horse or less were impossible to detect in blood and approached the limit of detection in urine, it is now possible to detect doses of acepromazine of as little as 0.1 mg/horse. Confirmation of such positives, however, depends on GC/MS identification of acepromazine and its metabolites in flagged samples, and this technology has not changed as dramatically as the detection technology.

RESERPINE

In contrast with the relatively short action of acepromazine, reserpine is a very long acting tranquilizer, with a duration of action of up to ten days, or possibly longer, after a single dose in the horse. This long duration of action has long been known among horsemen who referred to reserpine as the ten day tranquilizer. Clinically, however, if one doses a horse with reserpine, the horse would be clinically normal within about three days

of dosing, and would easily pass clinical examination as a "normal" horse. On the other hand, people familiar with the horse would be able to detect subtle changes in the horse's behaviour long after the clinical signs of "reserpinization" had worn off, and the drug was used for this effect under certain circumstances.

The clinical signs of "reserpinization" in the horse are clearcut. The initial signs are sweating over the shoulders, back, stifle and between the legs. The horse begins to pass increased amounts of gas and then diarrhoea commences. The faeces become soft, liquid, and cow-like, and remain liquid for two to three days. The horse stands in a dejected attitude, the upper eyelids droop and if the horse is a male, the penis may be extended for between ten and twenty hours. If the animal is acutely sensitive to reserpine, it may show signs of colic and go down for a short period. However, by two to three days after dosing most of these clinical signs will have disappeared and the animal will appear clinically normal and be difficult to distinguish from an untreated animal. If the dose of reserpine is small, (about 1-2 mg/horse) the clinical signs are much reduced and the horse may appear clinically normal in 24 to 48 hours (Tobin 1978).

When we tested the effects of reserpine in our variable interval responding apparatus, we found that the central effects of reserpine were very marked and lasted for long after the clinical signs of "reserpinization" had disappeared. As shown in Figure 3, the

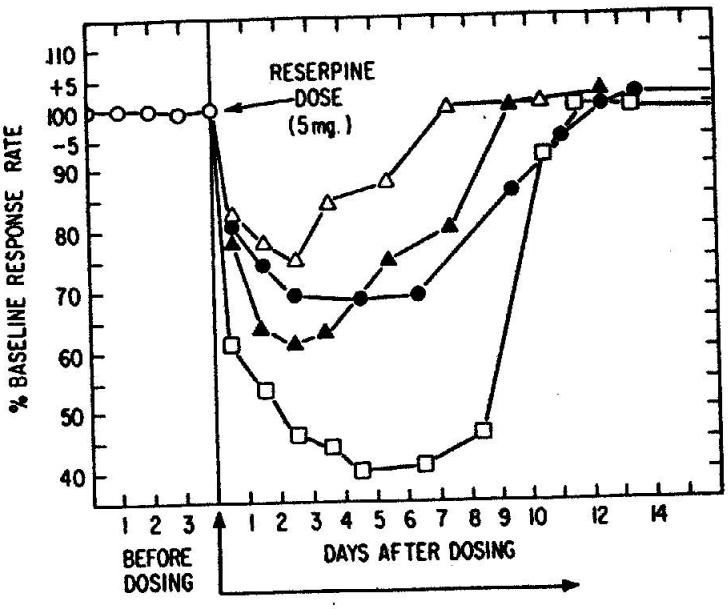

Figure 3:
Effects of reserpine on vi-60 schedule in 4 horses. The operant-behavior rates of 4 horses were normalized as 100% for 5 days before dosing. The symbols show the changes in responding rate observed in 4 horses after administration of 5 mg of reserpine IV to each horse at the indicated time. Reproduced with permission from Charles C. Thomas, Publisher.

behavioural effects of reserpine took between three and six days to peak and between seven and ten days to come back to control values (Shults *et al* 1982). These results, which show that the behavioural effect of reserpine last for much longer than the clinical effects of reserpine, and support the contention of horsemen that reserpine has long lasting tranquilizing effects in the horse.

The reason for the long lasting actions of reserpine is likely to be the long half-life of this drug in the horse. While definitive experiments have not been performed in the horse, the half life of this drug in the human is about ten days (Maas *et al* 1969) and early thin layer chromatographic work in the horse has shown that the drug is detectable in the plasma of horses for at least five days. More recently, we have developed an ELISA test for this drug and have detected reserpine in the urine of horses for prolonged periods after administration of this drug (Woods *et al* 1989). As shown in Figure 4, reserpine is detectable with this technology for up to 4 days in serum and for even longer periods in urine. Again, as with most of these sensitive immunoassay tests, the determining factor in the period for which these drugs can be detected is not the immunoassay test but the sensitivity of the confirmation methods.

In summary, therefore, reserpine is a drug that has very subtle and long lasting behavioural effects in the horse. After administration of a 5 mg dose of this drug to a

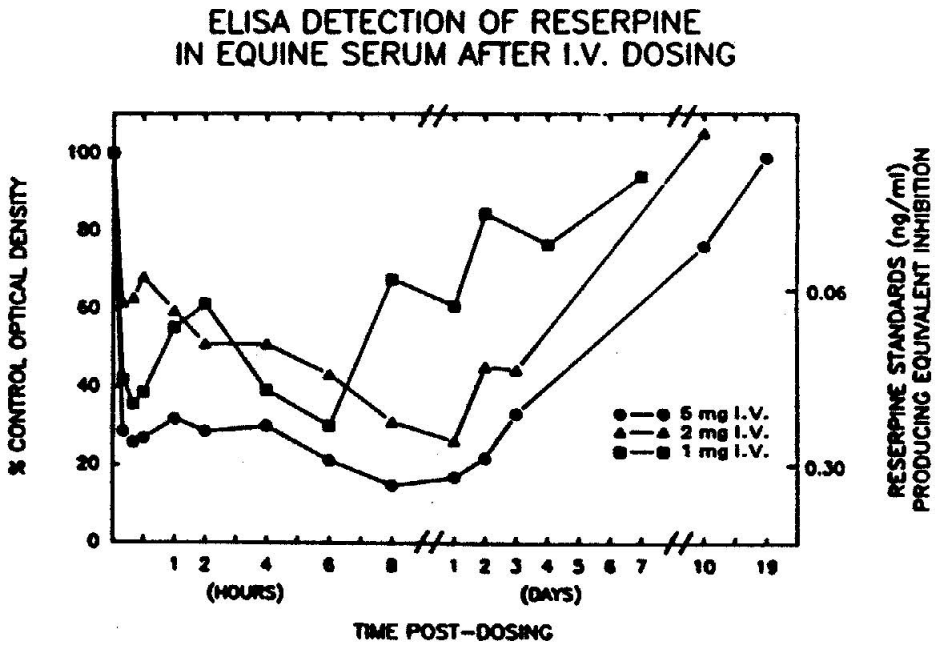

Figure 4:

ELISA detection of reserpine in equine serum samples following IV administration of 1, 2, and 5 mg per horse. The left hand column shows the percent of control optical density and the right hand column shows the equivalent inhibition produced by reserpine standards. Reproduced with permission from *Res. Comm. Chem. Pathol. Pharmacol.*

horse, the behavioural effects take up to five days to peak and can last for up to ten days. The clinically observable effects, however, are much more short-lived and are essentially over within a period of about two days.

DETOMIDINE

Detomidine (Domosedan®), 4(5)-(2,3-dimethylbenzyl) imidazole hydrochloride, is a novel non-narcotic sedative analgesic. The manufacturers (Farmos Group Ltd., Turku, Finland) are seeking to gain approval of detomidine for use in the veterinary pharmaceutical market in the United States. It is currently being used clinically in Europe and is suspected of being illegally administered to performance horses in the US.

Detomidine is pharmacologically related to the widely used sedative xylazine, in that both are alpha-2 adrenoreceptor agonists causing sedation by decreasing the overall vigilance of the animal (Ruskoaho 1986). Both have been classified as a sedative, analgesic and muscle relaxant. Detomidine is substantially more potent however, with comparable therapeutic doses of 10 mg/horse for detomidine compared to 500 mg/horse for xylazine (Jochle and Hamm 1986). In addition, detomidine appears to have a higher affinity for the alpha-2 receptors in the central nervous system (Ruskoaho 1986).

Several studies of the pharmacology of detomidine have been conducted in Finland as well as in the US. Detomidine is highly lipophilic and is rapidly absorbed after administration by either the IV and IM route (Jochle and Hamm 1986). It is distributed throughout the body and can readily pass the blood-brain-barrier. The full metabolic profile of detomidine in the horse has not been worked out at this time.

The principal physiological responses of note include transient effects of bradycardia with vascular hypotonus. Respiration is slowed initially with the effect being most pronounced in the first 5 minutes after injection and then is characterized by a gradual return to baseline levels. Hypoxia and cynosis can parallel this respiratory depression and apparently corresponds to the deeper analgesic and sedative effects. Substantial diuresis can occur after administration of detomidine with this effect being most pronounced at 1 to 2 hours post injection. Other side effects such as muscle tremors and sweating can also occur in animals administered doses at the therapeutic or higher level (Wood *et al* 1988).

The sedation and analgesia produced by detomidine allows for a wide range of manipulations and is thought to occur due to its potent and specific agonism for alpha-2 receptors in the central and peripheral nervous systems. It has been shown to produce a stable level of sedation and analgesia while not rendering the animal recumbent (Wood *et al* 1988). The pharmacological characteristics of detomidine indicate that it would be quite efficacious for use in the examination or manipulation of fractious animals, minor surgery, and relief or control of symptoms of colic and for the sedation of animals prior to translocation. The use of detomidine is likely to be widespread in the US when it is granted FDA approval.

THE MINOR TRANQUILIZERS; CHLORDIAZEPOXIDE AND DIAZEPAM

Chlordiazepoxide (Librium®, Roche Laboratories, Nutley, NJ) and diazepam (Valium®, Roche) have been extremely popular in the human market as anxiolytics and have similarly been used in equines for their tranquilizing and antiepileptic actions (Tobin 1981). While it is obviously difficult to characterize the anxiolytic effects of these drugs in the horse, they have clearcut pharmacological effects, acting in large doses to interfere with spontaneous locomotor activity, with the horse being clearly depressed, showing a reduced respiratory rate and obvious muscle relaxation.

Despite these effects on the appearance and behavior of horses, the acute effects of an IV dose pass, and the horses are well coordinated and alert at thirty minutes after dosing. Surprisingly, when we challenged these horses with fentanyl, we obtained the full locomotor response that we would have observed in the absence of diazepam or chlordiazepoxide (Figure 5) (Tobin 1981). This came as a surprise to us since based on the depression seen in these animals, we would clearly expect some depression of the locomotor response.

In man, the plasma half-life of diazepam is relatively long with a half-life of the drug of from two to three days. In the horse the half-life of the drug is clearly shorter, with the drug being detectable in blood for twenty four hours after a single IV dose to a horse. Diazepam appears to be extensively metabolized in the horse, and detection of the parent drug has not reported in the urine of horses. Because these metabolites have been found in the urine of horses for up to 48 hours after the last dose, the minimum clearance time period that should be allowed for this drug in the horse is about 48 hours.

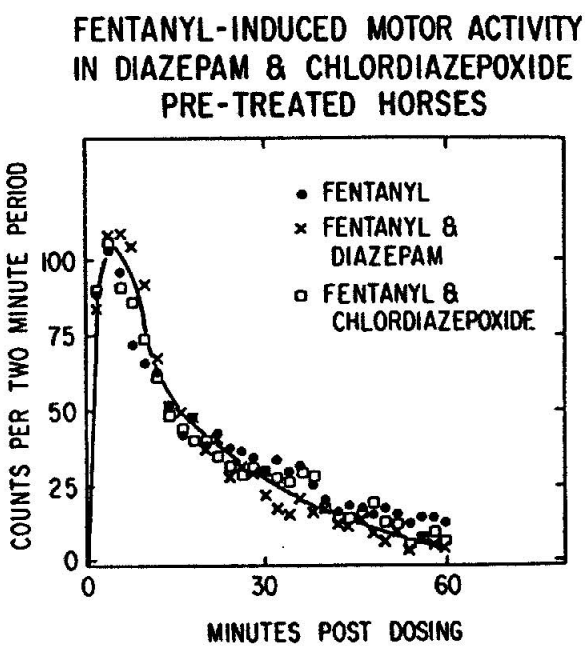

Figure 5:

Lack of effect of diazepam and chlordiazepoxide on fentanyl-induced trotting in horses. Horses were dosed with 0.1 mg/kg (250 mg/1000 lb) of diazepam or 0.2 mg/kg (200 mg/1000 lb) of chlordiazepoxide and then challenged with about 8 mg of fentanyl. The solid circles show the trotting response to fentanyl, while the crosses (x) show the response in the presence of chlordiazepoxide and the open squared (□) the response in the presence of diazepam. Diazepam did not affect the trotting respone to fentanyl, while a small but statistically significant inhibition was seen after chlordiazepoxide. Reproduced with permission from Charles C. Thomas, Publisher.

In summary, the minor tranquilizers are a group of drugs about which relatively little is known concerning their pharmacology in the horse. They have clearcut depressant actions and a relatively long plasma half-life in the horse, but no definitive measurement of their pharmacological effects and duration of action in the horse has been made. They are not found in equine urine in the unchanged form, and at least 48 hours should be allowed after administration of one of these agents for the urine of the horse to clear the drug.

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