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Performance testing in horses: a review of the role of simple behavioral models in the design of performance experiments

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To optimize the design of performance experiments, detailed information about the pharmacology of the drug used for trial in the horse is required. The optimum dose of drug to use, the time of peak drug effect, and the reliability of the response needs to be known in order to confidently design and interpret performance experiments.

By the use of a simple step counting model, the dose– and time–response relationships and the reliability of the locomotor response to narcotic analgesics can be readily determined. These data provide a good basis for dose selection for performance trials. On the other hand, this same experimental approach has shown that the reliability of the locomotor response to apomorphine is low, and that the locomotor response to butorphanol is small. The experimental model therefore suggests that these are not suitable drugs for performance trials.

Studies with variable interval responding apparatus have shown that individual horses can vary quite markedly in their sensitivity to some central stimulants. For these drugs, therefore, the dose to use in performance trials would also depend on the individual horse tested.

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The basic question which is asked in equine performance work is whether or not certain drugs or treatments have the ability to improve the performance of racing horses. The specific questions asked fall into two categories:

(i) will stimulant drugs, or narcotic analgesics, correct for deficits in motivation or courage of a less than first-class horse and enable it to perform better than it normally would?

(ii) given a top class and racing sound horse, will stimulants increase the performance of this animal beyond its best performance in the absence of drugs?

These are very difficult questions to answer experimentally. In this paper, we shall indicate why we think it is unlikely that we will ever get satisfactory answers to these questions, and shall also point out some of the pitfalls lying in wait for those who try.

The problem with this type of question is the difficulty of designing and executing an experiment which can answer the questions being asked. Normally, when one designs an experiment, one tries to arrange that the experimental baseline is as small as possible and the experimental variable (in this case, time to complete 1 mile) is as large as possible.

ensure that one can reliably operate within this optimal response window.

The problem, of course, is where to obtain information on this optimal response window for a given drug in a given horse. We believe that the only useful way to define this window comes from the use of simple behavioral models to characterize drug action in horses.

Our first experience with a simple behavioral model came about quite fortuitously. We had been treating horses with small doses of fentanyl* (Sublimaze) in classical performance trials. We used approximately 0.25–0.5 mg doses of fentanyl IV about 15–30 min 'pre-race'. The horses were timed over a one mile pace. These doses were approximately the same as those recommended for use in humans, and were reportedly being used illegally on the racetrack. We saw no behavioral or performance effects of these small doses on the pacers and after a while we more or less abandoned this particular line of experiments.

In later pharmacokinetic experiments with fentanyl, the dose was increased to about 4 mg, or ten times that of the performance experiments, to improve chances of detecting the drug. We were surprised to see very clear-cut behavioral signs in horses treated with this dose, the animals becoming quite excited and doing what a clinician would describe as 'stall-walking'. This locomotor response was quantified by counting the number of footsteps which the animal made with his left foreleg (Fig. 3). Experimentally, this is a very 'clean' method, with low baseline values of about 4 steps/2 min, and a peak response of more than twenty-five times this baseline. Use of this method enabled characterization of the locomotor response to fentanyl, and the method proved to be applicable to other narcotic analgesic drugs (Figs 4 and 5; Tobin, Combie & Dougherty, 1979).

Development of this very simple behavioral method of quantifying the actions of narcotics revealed a lot about the action of the narcotic analgesics in the horse. Firstly, the method

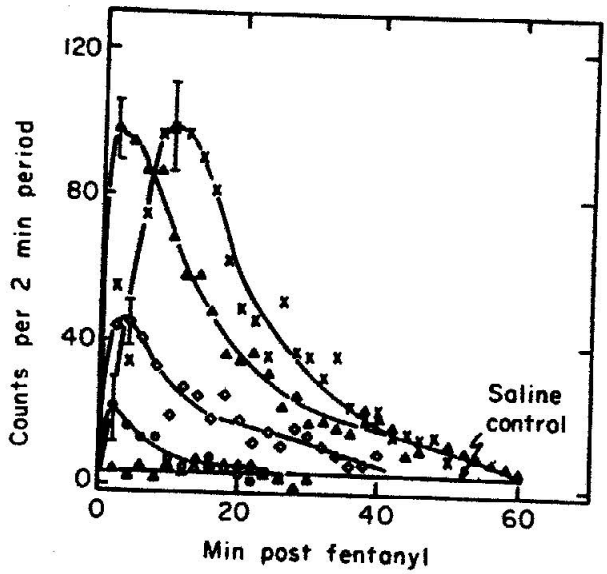

FIG. 3. Effect of fentanyl on spontaneous locomotor activity in four horses. Horses were injected with saline or increasing doses of fentanyl I.v. The average counts per 2 min period following saline injection are shown by the straight line near the bottom of the graph. The response to 0.001 mg/kg fentanyl is shown by the open triangles (Δ–Δ); 0.005 mg/kg by open circles (○–○); 0.010 mg/kg by open diamonds (◇–◇); 0.020 mg/kg by solid triangles (▲–▲); and 0.040 mg/kg by crosses (X–X). At the highest dose tested, all horses showed a loss of co-ordination resulting in a decrease in locomotion during the first 6 min. All points are the means of counts determined on four horses and the vertical bars represent SEMs. (Reproduced with permission of the Journal of Equine Medicine and Surgery.)

*Fentanyl (Sublimaze) is a potent, short acting narcotic analgesic which was reportedly widely used in racing horses.

demonstrated that locomotor stimulation is clearly part of the pharmacology of narcotic analgesics in the horse. The response was consistent, reliable, characteristic, and occurred after the administration of any narcotic analgesic. Response was rapidly and specifically blocked by narcotic antagonists. This was in sharp contrast with the previously 'known' view, that the responses of horses to narcotic analgesics tended to be erratic, with unpredictable components of depression and stimulation. Beyond this, some racing jurisdictions listed fentanyl as a depressant, which is understandable considering the lack of response to the small doses of drugs that are reportedly used in racing horses (Combie, Shults & Tobin, 1979).

The use of this simple behavioral model led to certain conclusions regarding doses and routes of administration for fentanyl. It became clear that for a reliable and reproducible stimulant effect fentanyl had to be given by rapid intravenous (i.v.) injection. With too large a dose, the horses became unco-ordinated and fell. The peak stimulant response occurred about 5 min after administration of the dose. When the drug was given subcutaneously, the response was erratic and less predictable. While the effects of intramuscular injection were not studied (the route reportedly used on the track), it does not appear likely that this method of administration would give rise to reliable or reproducible responses to fentanyl.

These studies resulted in the determination of the dose and route by which fentanyl should be given to attain the optimal response window. They also showed that the locomotor response to fentanyl was highly reliable and reproducible. As shown in Fig. 6, the fentanyl dose could be repeated within 90 min and produce almost the same maximal response. Additionally, the effect was quite reproducible

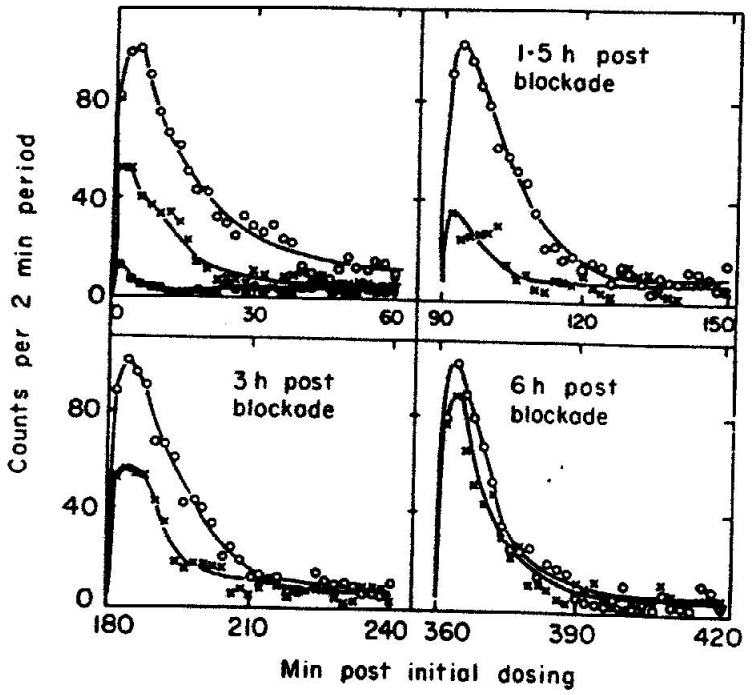

FIG. 6. Blockade of the locomotor response to fentanyl by acepromazine and naloxone. Horses were dosed i.v. with 0.1 mg/kg acepromazine or 0.015 mg/kg Narcan® at 15 and 5 min, respectively, before a series of four doses of 0.020 mg/kg fentanyl. The open circles (○–○) represent the locomotor response of horses dosed with fentanyl at 0, 90, 180 and 360 min. The crosses (X–X) show the response to fentanyl following pretreatment with acepromazine and the solid squares (■–■) show the response after pretreatment with naloxone. All points are the means of experiments on three horses. (Reproduced with permission from Combie *et al.*, 1981.)

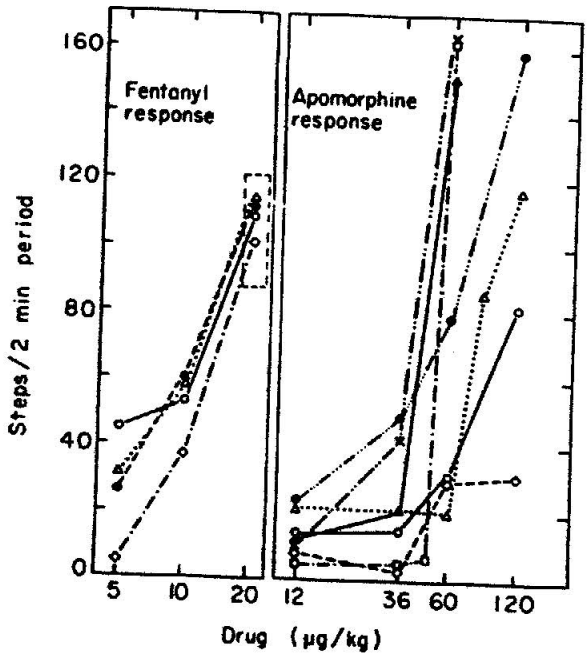

FIG. 8. Individual dose–response curves to fentanyl and apomorphine in the horse. The left-hand panel shows four individual dose–response curves to fentanyl obtained in a sequence of experiments. The consistent nature of the response to fentanyl is indicated by the dashed window. The right-hand panel shows all the dose–response data obtained with apomorphine, demonstrating the wide scatter in responses and the often very steep dose–response curves obtained with apomorphine. (Reproduced with permission from Tobin *et al.*, 1979.)

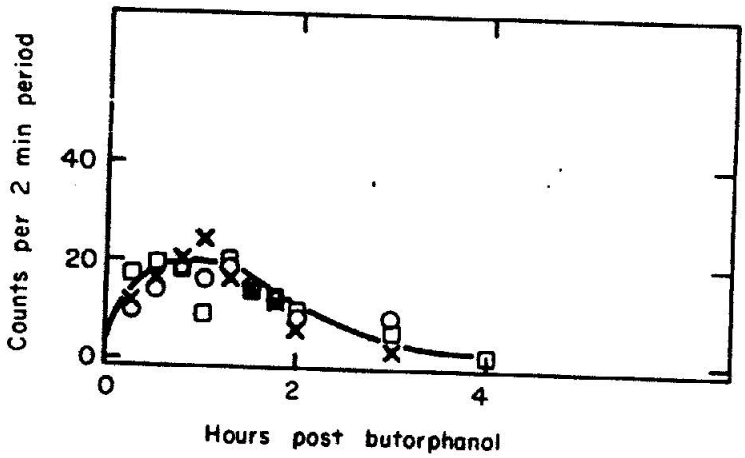

FIG. 9. Butorphanol-induced locomotor activity in horses. The symbols show the locomotor response to increasing doses of butorphanol (Stadol®). The peak locomotor response to butorphanol, at about 20 steps/min, was about one-fifth the maximal response following other narcotic analgesics (J. Combie and T. Tobin, unpublished experiment). (○) 0.1 mg/kg; (×) 0.2 mg/kg; (□) 0.4 mg/kg.

at about 15 min after methamphetamine administration (Fig. 11) and was detectable for about 2.5 h after the dose. Unfortunately this was a relatively laborious method of obtaining data points, the use of combinations of drugs requiring elaborate controls (Tobin & Woods, 1979).

By the use of drug combinations it may be possible to extend the range of drugs that can be covered by the simple step-counting model. Unfortunately, these modifications make the method quite cumbersome and much of the speed, simplicity and power is lost.

While the behavioral models described above worked well for stimulant drugs, because of their very low baselines, drugs, whose basic action was to depress activity, were not as well suited to study by these methods. For these drugs, another experimental approach was developed in co-operation with Dr John Dougherty of the Veterans' Administration Hospital. This approach used variable interval responding to quantify drug action (Shults, Combie, Dougherty & Tobin, 1979a; Shults, Kownacki, Woods, Valentine, Dougherty & Tobin, 1979b).

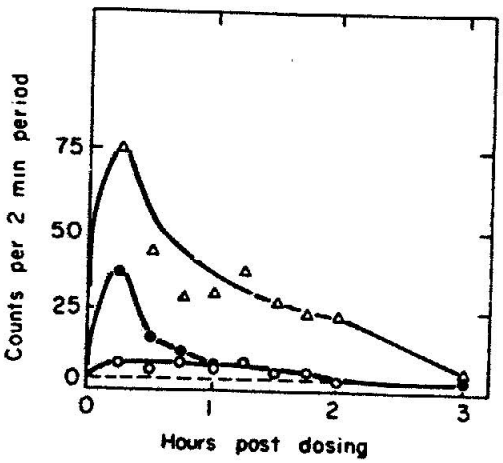

FIG. 11. Potentiation of locomotor response to fentanyl by methamphetamine. The open circles (○–○) show the locomotor response of horses after 0.25 mg/kg methamphetamine by rapid i.v. injection, while the solid circles (●–●) show the response after 0.020 mg/kg fentanyl i.v. The triangles (△–△) show the 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. (Reproduced with permission from Tobin & Woods, 1979.)

With variable interval responding apparatus (Fig. 12), horses were trained to break a light beam for rewards of 30 ml aliquots of oats. The horses did not seem to mind this apparatus as they galloped over to the experimenter when he appeared on the farm each morning. In these experiments, the schedule of responses was set up so that the times, when breaking the light beam would result in a reward, were randomized. The horses worked the apparatus at their own individual rates, which were always sufficient to ensure that the horses received the maximum number of rewards. This rate was quite sensitive to drugs as it was set by the horse itself and both stimulants and depressants produced substantial changes in the rates.

Once accustomed to this apparatus, the horse responded at its own individual rate, which was usually quite stable over time. Figure 13 shows the responding rates of four horses over a period of months. Generally the responding rates were quite stable over a number of experiments carried out during this period. Horses were routinely tested on the experimental system every other day providing that the control responding rate was within ±5% of the norm for that animal on 3 successive days.

This apparatus was used in two ways. With a long-acting drug, the animal was dosed and its response tested on each succeeding day. This approach yielded a time–response curve, and the prolonged pharmacological action of reserpine made it a classic drug for this type of experiment. The responding rate of horses dosed with reserpine (Fig. 14) dropped for 3–4 days post dosing to as low as about 50% of control values, and took up to 10 days to return to normal. Thus, this apparatus can be used to obtain both dose– and time–response data, making this a very useful model with long-acting drugs.

The 10 day duration of reserpine action was considerably longer than expected. Clinical signs of reserpinization usually disappear within 3 days after dosing, spontaneous locomotor activity returning to control values by the third post dosing day. While respected veterinarians have stated that the pharmacological actions of reserpine are over within 3 days, these experiments support horsemen's claims of a much longer action for this drug.

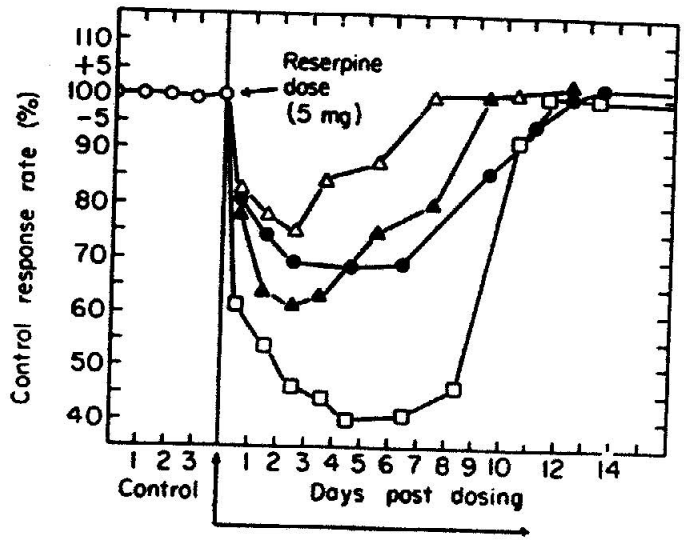

FIG. 14. Inhibition by reserpine of variable interval responding in horses. The open circles (○–○) show operant behavior, normalized as 100% for four horses for 5 days before dosing. The open squares (□–□), solid circles (●–●), and open (△) and solid (▲) triangles show the inhibition of operant behavior (tranquilization) in these horses after a single dose of 5 mg/horse of reserpine i.v. as indicated on day 0. (Reproduced with permission from Tobin, 1981.)

However, with a short-acting drug the power of this method is reduced. The experiment takes 30 mins to run and the period of action of many short-acting stimulant and depressant drugs in horses may be no longer than 2 or 3 h. Therefore, each experiment produces only one time or concentration point and the construction of complete dose– and time–response data, so readily obtained with the step-counting method, can be very laborious indeed.

Therefore, we estimated the time of peak drug action from effects on physiological parameters (i.e. respiration), and then studied the action of different drug doses at the times of peak effect. Most commonly, the animal was dosed i.v. and placed into the responding apparatus within 30 min, when the effects of drug administration on the responding rates were measured (Gabriel, Henderson & Smith, 1963; Tobin, 1981).

Figure 15 illustrates the effects on response rate of different doses of cocaine administered i.v. Two characteristics show up clearly in this data and both are well known from our everyday experience. Firstly the response to stimulants is biphasic, in that each horse received a dose which produced maximal stimulation, but beyond which the responding rate was reduced (Shults *et al.*, 1979b).

Secondly, and equally important, the dose required to produce peak stimulation varied markedly among horses, for example in one horse 4 mg of cocaine was sufficient to produce this effect, while for another horse about 250 mg was required. The obvious problem for the investigator carrying out a performance study, on for example six horses, is the dose to select. Ideally for a stimulant effect, each horse should be tested individually and the dose varied as necessary.

Broadly similar results were obtained with methylphenidate (Fig. 16), although with this drug the results showed more distinct stimulation and less variability. Methylphenidate was unusual in that its administration produced up to 600% stimulation in responding activity. Furthermore, less individual variation was observed in the dose for peak response with methylphenidate than with cocaine (Shults *et al.*, 1979a). The data suggest that methylphenidate would be a more satisfactory drug to use in performance trials than cocaine, as consistent stimulation is easier to produce in a group of horses with methylphenidate.

Therefore, variable interval responding is

another useful method for defining the action of centrally acting drugs in horses. By use of this method, dose–response or time–response studies on stimulant and depressant drugs can be carried out. The drug responses can be characterized in horses and substantial individual variation can be demonstrated between horses in their response to these agents. As drug doses which stimulate one horse may act to depress desired behaviors in another, such studies can be useful in screening both horses and drugs for use in performance trials.

In conclusion, the use of simple behavioral models provides substantial information on specific characteristics of drugs and the individual horses in which they are used. This information may be necessary for the design of useful performance studies. Similarly, our experience suggests that certain horses respond more consistently than others. Performance trial designs can be improved by using this data to increase the probability of these studies generating scientifically useful data.

The ultimate performance trial, designed to discover whether a sound, high performance racehorse will run faster on a stimulant than without, is unlikely to be performed, as such horses are generally unavailable for experiments. The question of whether the best performance of horses available for experiments can be improved by stimulant drugs is also largely unanswered. Most of the performance work done with these horses has been in gallop or canter trials and not, to our knowledge, in simulated races. Most of the performance work to date has been with horses running slower than their maximum capability. These experiments have shown, that horses can be stimulated by drugs, but they have not shown that their best performances can be improved (Fujii, Senji, Inada, Shichiro, Yoshida, Shirgeru, Kusanagi, Chiyoko, Mima, Kyosuke, Natusuno & Yoshihiro, 1974; Sanford, 1971, 1973; Stewart, 1972).

Another problem with performance experiments is that the results will have no practical application. If drugs are stimulants, they are banned. This ban is a societal judgment and is not seriously questioned. Negative data in performance experiments is unlikely to lead to changes in the use of stimulants in racing horses, while positive results will only serve to reinforce the current position.

There is critical need for studies to determine when the pharmacological action of a drug is over. As some stimulants, and especially tranquilizers, narcotics and local anesthetics, have legitimate medical uses, pharmacologically insignificant traces of these drugs can be expected to show up in horse urine for quite long periods (Tobin, Combie & Nugent, 1981). In the field of equine forensic chemistry, an important contribution of pharmacology is to characterize the actions of these drugs and to show when they cease.

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