NARCOTICS AND STIMULANTS: HOW THEY AFFECT HORSES

T. TOBIN AND W. E. WOODS

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SUMMARY

The narcotic analgesics have a characteristic pharmacology in the horse that makes them very useful drugs in racehorses. In general, the μ agonist narcotics produce locomotor responses and autonomic stimulant effects that are very characteristic and easily quantifiable. One can quantitate the actions of the narcotic analgesics by measuring the number of footsteps produced by a given dose of drug. Using this simple technology one can produce dose and time response curves for individual narcotic analgesics in the horse, and accurately compare the potency and duration of actions of these drugs. Using this technique, it appears that all the narcotic analgesics produce virtually the same spectrum of pharmacological effects in the horse. The locomotor response to narcotic analgesics can be used to measure the actions of certain stimulant drugs. When a stimulant is given to a horse in addition to the administration of a narcotic analgesic, the locomotor response is enhanced and prolonged. Stimulant drugs for which this response has been observed include caffeine and the amphetamines.

Another technique used to determine the actions of stimulant drugs is variable-interval responding employing an operant conditioning apparatus. Horses trained on this apparatus and exposed to various stimulants are known to improve their response. The increased variable-interval response to cocaine was found to be significant but variable between horses, while the response to methylphenidate was both larger and more predictable between horses.

THE NARCOTIC ANALGESICS

When an opiate drug is given to man it produces a classical spectrum of pharmacological effects, including analgesia, sedation, and respiratory depression. In the horse the spectrum of pharmacological effects that opiates produce are quite different, in that they include locomotor stimulation (Figure 1) as well as analgesia, and narcotic analgesics have little effect on respiratory depression until much higher doses of drug are attained. These are unexpected effects for a group of drugs that are thought of as

depressants in man, but the effects are clearcut and have been observed with all of the classic μ agonist narcotic analgesics that we have studied in the horse (Tobin 1981).

Figure 2 shows a series of dose/locomotor response curves for the various narcotic analgesics that we have tested in the horse (Kamerling *et al* 1989). The most potent

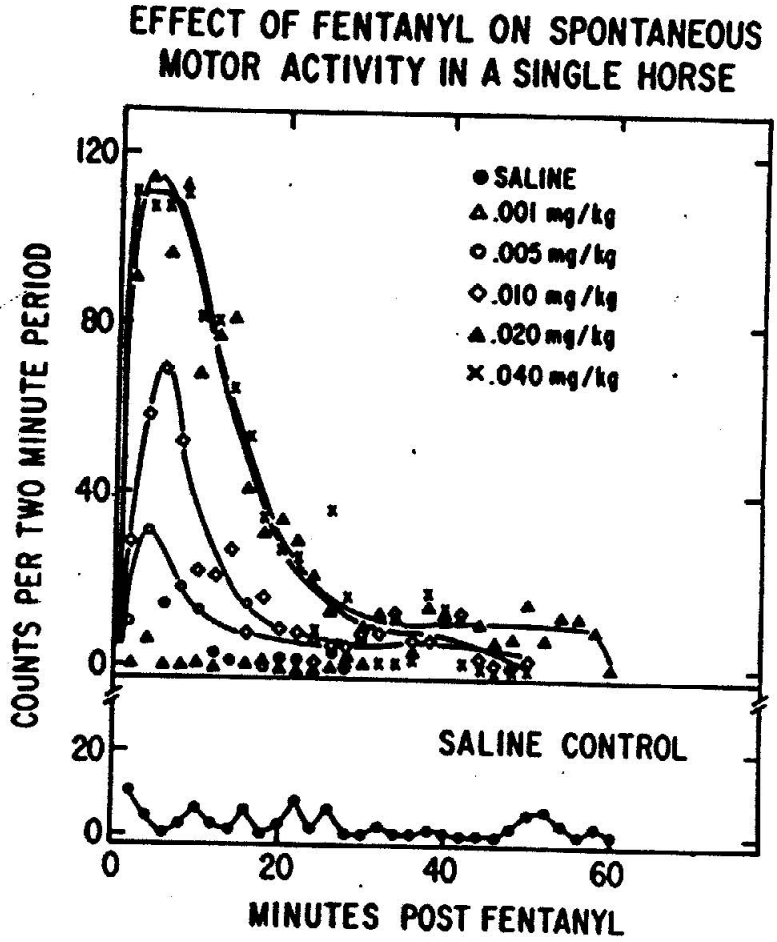


Figure 1:

Effect of fentanyl on locomotor activity in a single horse. A horse was injected with saline or increasing doses of fentanyl IV. The number of times the horse lifted its left front foot and placed it in a different position in a two-minute period was recorded as an indication of locomotor activity. Activity following IV saline injection is shown by solid circles (●-●); 0.001 mg/kg fentanyl by open triangles (Δ-Δ); 0.005 mg/kg by open circles (O-O); 0.010 mg/kg fentanyl by open diamonds (◊-◊); 0.020 mg/kg fentanyl by solid triangles (▲-▲); and 0.040 mg/kg fentanyl by crosses (X-X). Reproduced with permission from *J. Equine Med. Surg.*

member of this group that we have tested for action in the horse is etorphine or "elephant juice". Etorphine begins to produce its pharmacological response at doses of less than 10 μg/horse and a dose of 100 μg/horse produces a good locomotor response. Carfentanil, an analogue of fentanyl, produces the next most potent pharmacological response, followed by sufentanil and fentanyl. Additionally, as shown in Figure 2, all of the narcotic analgesics tested showed essentially equivalent peak locomotor responses with approximately parallel dose response curves for most of the drugs tested. However, in the case of partial agonists, such as pentazocine and ethylketazocine, the dose-response curves are not parallel, indicating a different type of receptor interaction for these agents.

It is probably worth pointing out that this was an extremely reliable pharmacological response, which could be obtained repeatedly and very reproducibly in our experimental horses. For example, if we dosed a horse repeatedly with fentanyl, the locomotor response could be obtained approximately every ninety minutes, and changed very little over the period of the experiment. In fact, as we will show later, one can use this response to accentuate or develop the effects of other stimulant drugs, or conversely, to show the effect and duration of action of depressant or blocking agents (Figure 3). Its simplicity and ease of evaluation makes this a very valuable technique, and one which we have used repeatedly in our work with drugs acting on the central nervous system of the horse (Combie *et al* 1979).

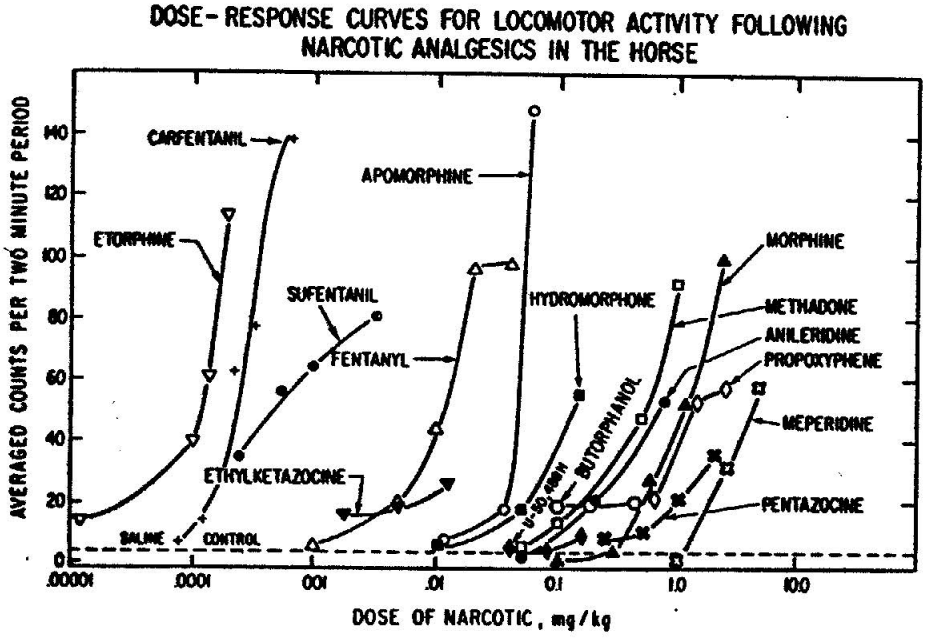


Figure 2:

Locomotor effects of selected narcotics in the horse. The symbols show the peak locomotor responses, as steps/2 minutes after rapid IV injection of the indicated doses of each agent. Apomorphine, not a narcotic analgesic, is included for comparative purposes. Reproduced with permission from *Equine Vet. J.*

The ability of narcotic analgesics to produce central nervous system stimulation and locomotor effects is clearly potentially useful in a racing horse. A horse that is subclinically lame, for example, would be helped by both the analgesic effect of these

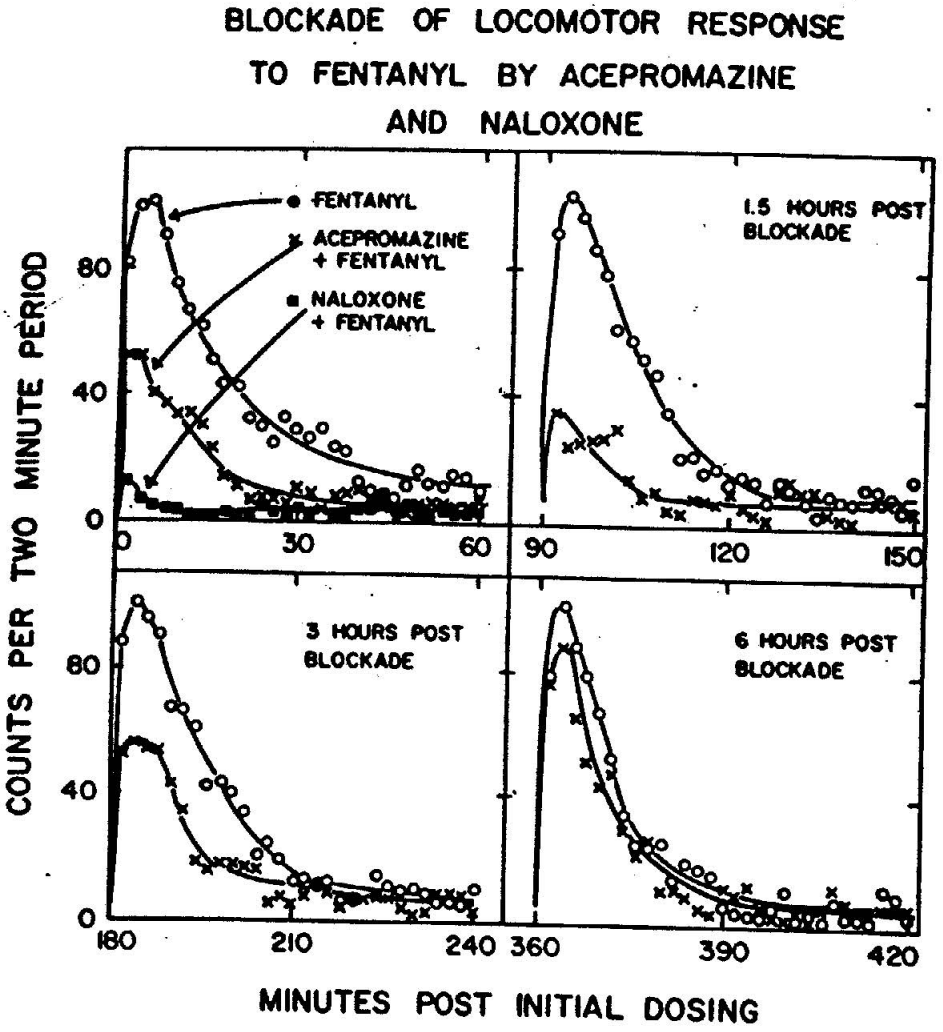


Figure 3:

Blockade of the locomotor response to fentanyl by acepromazine and naloxone. Horses were dosed IV with 0.1 mg/kg acepromazine or 0.015 mg/kg naloxone at 15 and 5 minutes, respectively, before a series of 4 doses of 0.020 mg/kg fentanyl. The open circles (0-0) represent the locomotor response of horses dosed with fentanyl at 0, 1.5, 3 and 6 hours. The crosses (X-X) show the response to fentanyl following pre-treatment with acepromazine or naloxone. All points are the means of experiments on three horses.

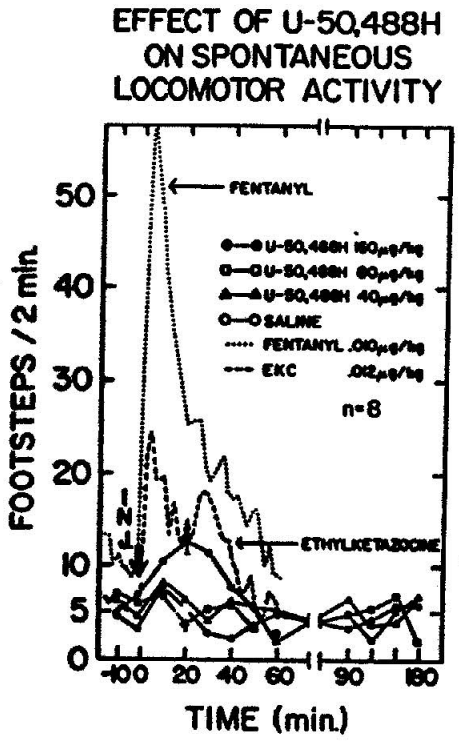
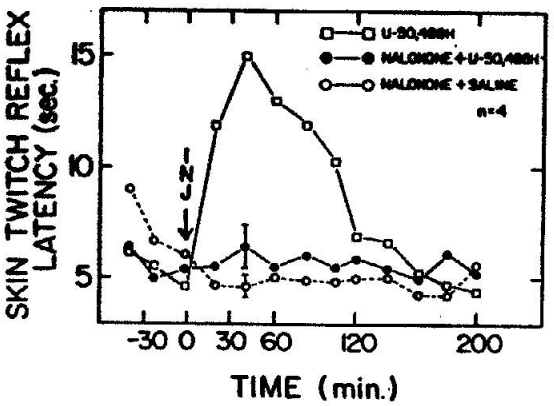


Figure 4:

Locomotor and analgesic effects of selected narcotics.

◀ **Panel A.**

Spontaneous locomotor activity after fentanyl, ethylketazocine and U-50,488H. The dotted line (....) shows the locomotor response of four horses after the medicated dose of fentanyl was administered IV. The dashed line (----) shows the response after the indicated dose of ethylketazocine, while the symbols show the response observed after the indicated doses of saline or U-50,488H. Reproduced with permission from *Equine Vet. J.*



◀ **Panel B.**

Analgesic effect of U-50,488H and its antagonism by naloxone. The open squares (□-□) show the analgesic response to U-50,488H after IV administration of 160 µg/kg, in the presence of naloxone, 20 µg/kg (●-●) administered IV 5 minutes prior to U-50,488H. Reproduced with permission from *Equine Vet. J.*

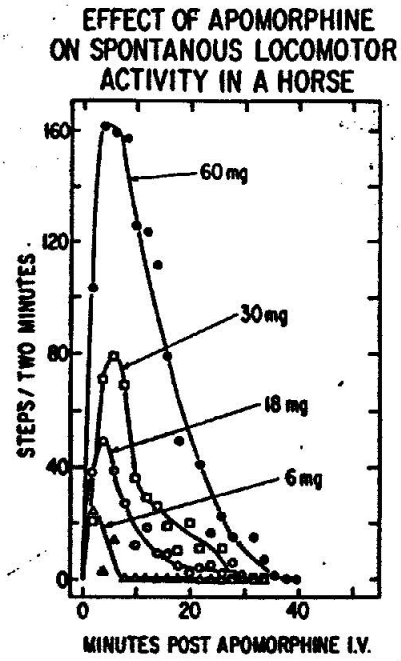


Figure 5:
Effect of apomorphine on spontaneous locomotor activity in the horse. A horse was injected intravenously with either 6 (△-△), 18 (○-○), 30 (□-□), or 60 (●-●) mg of apomorphine. The symbols represent the number of steps/2 minute period postinjection. Reproduced with permission from *J. Equine Med. Surg.*

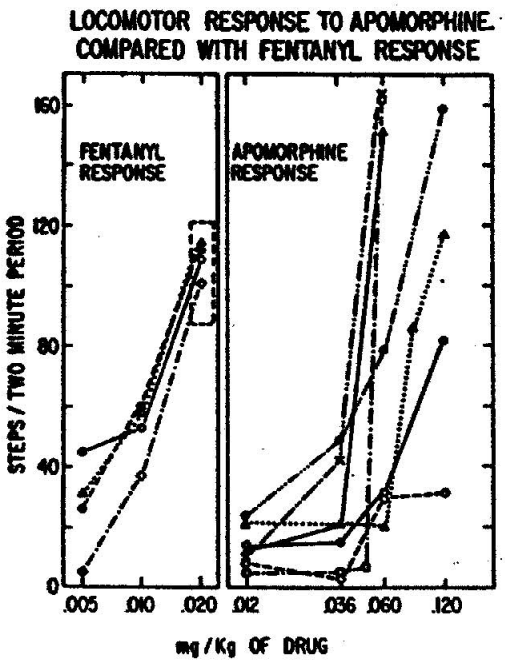


Figure 6:
Individual dose response curves to fentanyl and apomorphine in the horse. The left-hand panel shows four individual dose-response curves to fentanyl obtained in a sequence of experiments. The consistent nature of the response to fentanyl is indicated by the dashed window and has been seen repeatedly in other experimental work. The right-hand panel shows all the dose-response data obtained with apomorphine, demonstrating the wide scatter in responses and the sometimes very steep dose-response curves obtained with apomorphine. Reproduced with permission from *J. Equine Med. Surg.*

drugs and by their locomotor stimulant effects. Beyond this, it appears that the stimulant drugs are likely to potentiate these actions of the narcotic analgesics and add to the locomotor and analgesic effects of these drugs.

From the point of clinically effective analgesia the ideal agent would have the pain suppressant effects of the narcotic analgesics but without the locomotor or autonomic stimulant effects generally associated with this group of agents. Following this approach, we compared the locomotor response to kappa agonists with the analgesics effects produced by these agents. We chose the kappa agonists because this group of agents are known in other species to produce little excitation and good analgesia. As shown in Figure 4, the pure kappa agonist U50, 488H produced a very good analgesic response with little central excitation or locomotor response, suggesting narcotic analgesics from families other than the μ agonist family have the potential to be clinically useful narcotic analgesics in the horse (Kamerling *et al* 1988).

This footstep counting method also works very well with apomorphine, which has a long history of being used in racing horses (Tobin *et al* 1979). When we injected horses intravenously with apomorphine, we observed a very sharp increase in locomotor activity, broadly similar in nature to the response to the narcotic analgesics (Figure 5). The response is different to that of the narcotic analgesics in that it does not show the same ceiling response that the locomotor response to the narcotic analgesics does, but rather continues to develop as the dose is increased. In fact the limiting factor in these experiments was the rate of collision of the horses with the stall walls. Additionally, horses on apomorphine showed a typical snorting behaviour, a sound which in our experience is characteristic of horses treated with apomorphine.

Another characteristic of the response of horses to apomorphine was its unreliable or erratic nature. While the response of horses to narcotic analgesics was extremely reliable, could be elicited repeatedly, and always yielded virtually the same response, the response to apomorphine was very different indeed (Figure 6). In our hands the responses to apomorphine were always erratic, and we could not reliably repeat or predict the responses of individual horses to apomorphine. Despite substantial effort to determine the basis for these erratic effects, we were unable to identify their cause or causes.

THE STIMULANTS

Continuing our work with this simple footstep counting method, we explored its ability to detect the stimulant actions of other drugs, such as the amphetamines. We were, however, surprised to find that the method did not work with most stimulant drugs. For example, when the actions of amphetamine and methamphetamine were studied, we were surprised to find that injection of these drugs had virtually no effect on the locomotor response of horses, and certainly nothing comparable with the dramatic actions of opiates and apomorphine (Tobin and Combie 1982). We carried out a number of studies on horses with the adrenergic stimulants searching for simple behavioral models which would allow us to easily quantitate the stimulant actions of these drugs, but could find no such model. We therefore looked at the effects of combinations of drugs, using the narcotic analgesics as baseline stimulants and studying the effects of other stimulants added "on top" of the adrenergic stimulants.

When we pre-treated horses with caffeine and then injected them intravenously with fentanyl, we observed a clearcut stimulation of the horse when compared with the effect of fentanyl alone (Figure 7). The effect was most marked at the tail of the locomotor response

curve rather than at the early peak portion of the curve, and took the form of a heightened and prolonged "die-out" of the locomotor response curve. Nevertheless, the effect was clearcut, statistically significant, and is one of the few ways in which one can quantitate the stimulant effects of drugs, such as caffeine and the amphetamines, which in and of themselves do not produce clearcut locomotor responses or other easily quantifiable behavioral effects (Greene *et al* 1983).

Another method which we used to determine the actions of stimulant drugs was variable-interval responding. This technique allows one to accurately measure small changes in the behaviour of a horse and is one of the most sensitive behavioral monitoring techniques used in equine research (Shults *et al* 1982). Using this approach, we have investigated the actions of various stimulant and depressant drugs in the horse. Additionally, and more importantly, we have been able to investigate the behavioural

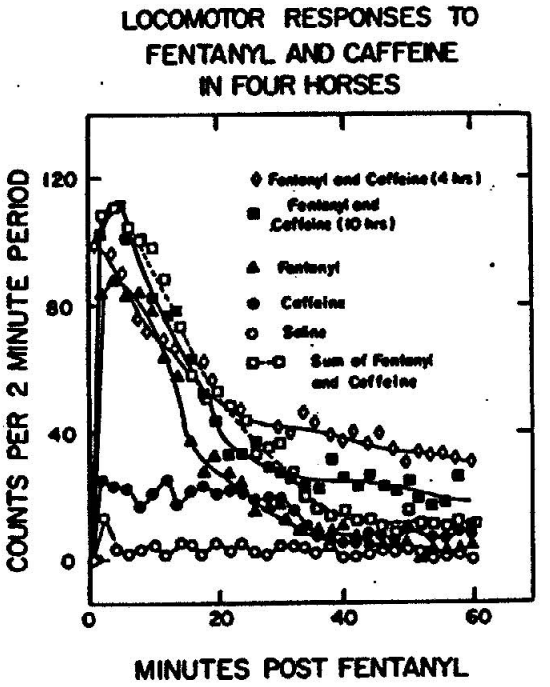


Figure 7:

Locomotor response (No. of footsteps/2-min period) in horses given fentanyl and caffeine. Caffeine (4 mg/kg) in a sodium benzoate solution was injected IV and after 15 minutes, 0.01 mg of fentanyl/kg was injected; the latter was time zero. The locomotor response was recorded 60 minutes. The symbols show the mean response of the 4 horses tested. Fentanyl was administered again at various time intervals including 4 hours (◊) after caffeine administration and at 10 hours (■) after caffeine administration. For comparison, the locomotor responses after the following independent drug administrations were recorded; saline solution (○),caffeine (●), fentanyl (▲), and the summed responses of caffeine and fentanyl (□). Reproduced with permission from *Am. J. Vet. Res.*

effects of different drugs in the horse to determine whether or not these agents have any significant behavioral effects in the horse. Information of this nature can be critical when it comes to making regulatory decisions about the use of certain drugs in racing.

Some of our first experiments in this area were performed with cocaine in an attempt to quantify the pharmacological effects of this drug in horses (Figure 8). When we dosed horses with cocaine we found that the response to the drug was biphasic, in that small doses stimulated the horses and larger doses depressed them (Shults *et al* 1982). This is a characteristic response to stimulant drugs, since small doses of a drug will increase a response, but larger doses will, by over-stimulating the horse, lead to a reduced response. This is somewhat the same as happens in humans, where one cup of coffee will produce a pleasant and useful stimulant effect, but two or three cups will render the individual uncoordinated and lead to reduced effectiveness.

As well as showing a biphasic response similar to the one that we see in the human, our horses also showed remarkably different sensitivities to cocaine. As shown in Figure 8, some horses were exquisitely sensitive to cocaine, with doses of about 4 mg/horse producing the peak stimulation of responding rate, while others were much less sensitive to this drug and required substantially more drug to produce the same pharmacological response. The take home message from this data is that, for at least some drugs, the dose that is required to stimulate some horses will have no effect in other horses and, conversely, doses that produce maximal stimulation in some horses will have no significant effect in other horses. Thus the successful use of stimulant drugs in racing horses requires a good knowledge of the pharmacology of the drug in the horse, and also for at least some horses, the drug's actions and the sensitivity to the drug of the particular horse being tested.

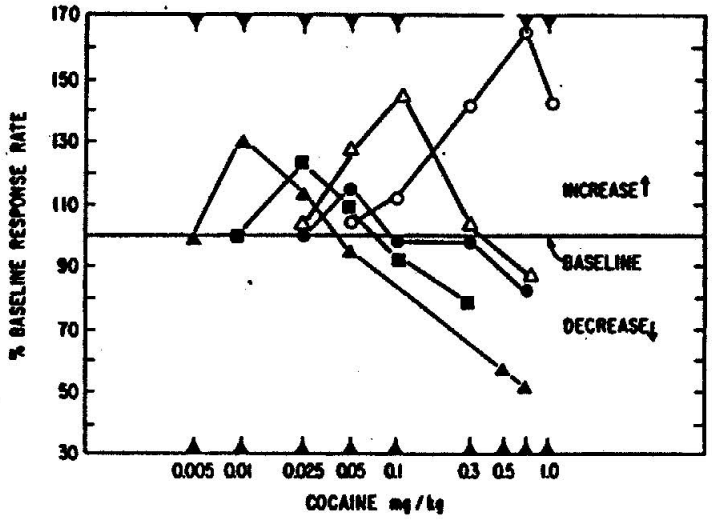


Figure 8:

Acute effects of cocaine on variable-interval responding schedule. The symbols represent the percentage of change in responding rates from control for each animal as the dosage of cocaine was increased. Reproduced with permission from Charles C. Thomas, Publisher, Springfield, Ill.

One stimulant drug that has a long history of use in the United States in racing horses is methylphenidate (Ritalin®, Ciba Pharmaceutical Co., Summit, NJ). When we tested methylphenidate in our behavioral responsing apparatus, the responses found were very interesting and of a nature that would suggest that it might be a useful drug in racing horses (Figure 9) (Shults *et al* 1981).

The first and most striking finding in the data was the exceptional stimulating efficacy of methylphenidate in the horse. Whereas cocaine could only produce a stimulant effect in the nature of twenty to thirty percent increase above baseline, methylphenidate produced a stimulation that ran to 700% above baseline in one case. In point of fact, the audible cue that accompanied each light break increased in rate so dramatically that it was immediately apparent to the observers that methylphenidate was a very effective stimulant drug in horses.

This effectiveness of methylphenidate as a stimulant drug in horses goes along with its efficacy in humans. The theory about methylphenidate in the human, where it is used in the treatment of attention deficit or hyperactive children, is that it acts to focus the child's activity and this, more than its stimulant actions, is what gives rise to the beneficial effects

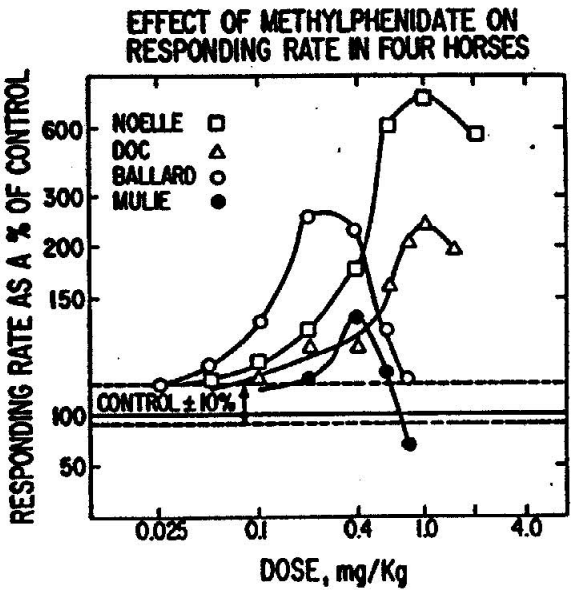


Figure 9:

Effect of methyphenidate on responding rate in four horses. Four horses were dosed with the indicated amounts of methylphenidate intravenously and introduced to the responding apparatus 20 min later. The symbols show the percentage change in rate for each 30 min session after administration of the indicated dose of methylphenidate to each horse: (□) Noelle; (△) Doc; (○) Ballard; (●) Mulie. Each experiment was performed between 10 and 12 a.m. on consecutive days and horses were treated with saline and allowed to return to their control responding rates between tests. Reproduced with permission from *J. Vet. Pharmacol. Therap.*

of this drug (Oettinger and Majovski 1976). Similarly, in the horse, it appears that, as well as being a stimulant, methylphenidate focuses the actions and attention of the horse and allows the horse to attain very high responding rates.

As well as giving rise to high responding rates, methylphenidate appears to be a drug to which horses respond predictably. Review of the data of Figure 9 shows that stimulant responses to methylphenidate all occurred over a relatively narrow dose response range, in contrast with the actions of cocaine, which occurred over a much wider range. It is much more likely, therefore, that, if one dosed a horse with methylphenidate, one would obtain a stimulant effect in a given horse with the average dose of methylphenidate, in contrast with that found with cocaine where the effect would be stimulant in some horses, but over stimulant or sub-threshold in others.

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