# DETOMIDINE:A PRELIMINARY ANALYSIS OF ITS DURATION OF ACTION IN THE HORSE BY VARIABLE INTERVAL RESPONDING

By

Thomas Wood, Tim Weckman, John Dougherty[1], William E. Woods, and Thomas Tobin

Department of Veterinary Science
108 Gluck Equine Research Center
University of Kentucky
Lexington, Ky 40546-0099

[1]Veterans Administration Hospital
Lexington,Ky 40502

Running Head: Detomidine and variable interval responding

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Correspondence should be addressed to Dr. Tobin.

SUMMARY

Variable interval (VI) reinforcement scheduling is a specific type of operant conditioning that is sensitive to drug effects even when overt clinical signs of the drug have diminished. We conditioned six horses to break a light beam with a head-bobbing movement and reinforced this behavior with a reward of clean oats (approximately 30 mg/reinforcement). Initial training procedures included acclamation to the behavioral equipment and fixed-ratio reinforcement scheduling. To establish baseline rates of behavior the horses were converted to a variable interval (60 seconds) reinforcement schedule and were kept on this schedule for the remainder of the study. A within subjects cross-over design was used with three treatments counterbalanced with the six horses. Detomidine (40 μg/kg), xylazine (1.1 mg/kg) and saline (10 ml) were administered intravenously (IV) on Monday mornings with VI responding rates measured during a routine 30 minute session each day Monday through Friday. Responses and reinforcements were recorded and dispensed by use of an electromechanical relay system wired to an electric eye, an automatic feeder and a programming and recording system. Xylazine produced a small decrease in responding rates at 1 hr post dose, while detomidine treated horses showed a dramatic decrease in responding rates at 1 hr and a lingering effect at 24 hrs. No long range effects were seen with either treatment as all horses were clearly back to baseline responding rates at 48 hrs post dose.

INTRODUCTION

Numerous methods of behavior monitoring are well suited for quantifying obvious clinical effects of drugs but are not sensitive enough to detect subtle changes in behavior. Variable interval (VI) reinforcement scheduling however, is a specific type of operant conditioning that has been used for many years by behaviorists to monitor rates of behavior in laboratory animals(Seiden and Dykstra, 1977) . In this type of conditioning, the animal is first trained to perform a task for an appropriate reinforcement. The animal is then switched to a program where responses are reinforced at variable times so the animal does not know when a response will elicit a reward. Adaptation to this VI reinforcement schedule produces baseline rates of behavior that can remain remarkably stable over time. Rates of behavior have been shown to be an effective measurement of subtle central nervous system depression or excitation in laboratory animals and recently has been shown to be effective in the horse. (Tobin and Combie, 1982, Shults et al, 1982).

An example of a drug that has been used for its subtle behavioral effects is reserpine. Reserpine has long been known to horse trainers as the "10-day tranquilizer", based on the subjectively measured effects of small doses of the drug in horses they have daily contact with (Tobin, 1981). Until the use of operant conditioning methods to quantify rates of behavior, such long term effects of reserpine could not be systematically detected in the horse. Operant conditioning studies using a VI schedule demonstrated that a dose of 5 mg

of reserpine per horse could suppress rates of behavior for up to 14 days (Shults et al, 1982).

Detomidine (Domosedan) is a new non-narcotic drug with potent tranquilizing, analgesic and sedative properties when administered to the horse (Jochle and Hamm, 1986, Clark and Taylor, 1986, Szeligowski et al, 1986) . Chemically, detomidine is [4(5)-(2,3-dimethylbenzyl) imidazole hydrochloride] (Lajunen and Roustsalaineen, 1984). Because the widely used sedative xylazine (Rompun) and detomidine are closely related in their pharmacodynamic properties, xylazine was included in the study for comparison purposes. Both are alpha-2 adrenoreceptor agonists and effect sedation by decreasing the vigilance of the animal (Ruskoaho, 1986). In this study, we elected to investigate the potential of these agents to produce long term subtle effects in the horse by use of the VI method.

MATERIALS AND METHODS

A total of six horses weighing between 370 and 590 kg each and representing different ages and breeds were used (Table 1). These horses were routinely maintained on pasture and were brought daily to the research barn for the experimental sessions.

Operant conditioning apparatus

A light-activated feeding console was built into a corner of a box stall in the research barn. The feeding console consisted of a feed bucket and an electric eye that responded each time the light beam was broken by the movement of the horse's head. Details of the construction of this apparatus

are presented in Fig 1. Adjacent to this stall, a tack room was equipped with the automatic feed dispenser and the monitoring and programming equipment.

Programs and programming equipment

The horses were trained initially to break a light beam with a head-bobbing movement by reinforcing this behavior with approximately 30 mg of oats dispensed by an automatic feeder directly into the feed bucket. The ratio of responses to reinforcements was gradually increased from 1 to 1 to 10 to 1. Once the horses were clearly acclimated to this fixed-ratio schedule, they were switched to a randomly determined no-reinforcement schedule. In this schedule, a reinforcer was earned when a response was made any time after a no-reinforcement interval. After a reinforcer was earned, more oats could not be earned until another no-reinforcement interval had passed. The duration of the no-reinforcement periods were variable so the horse could not determine when a response would yield a reward. This schedule generated a stable baseline of responding rates unique for each horse. In the "variable-interval-60" schedule, the average duration of the no-reinforcement interval was 60 seconds. Consequently, at the end of a 30 minute session the horse would have earned approximately 30 reinforcements.

Drugs

Detomidine (Domosedan, Farmos Group Lt. Turku, Finland) , Xylazine (Cutter Laboratories Inc., Shawnee, Kansas) or saline were used as the treatments. The doses administered were 40 μg/kg for detomidine, 1.1 mg/kg for xylazine and 10

ml/horse for saline and all were given by rapid intravenous (IV) administration.

Experimental procedures

A complete within subjects design was used with treatments counterbalanced in a Latin-square cross over to eliminate carry-over or time related confounds. For the daily sessions, each horse was taken from its holding stall and placed in the operant conditioning stall for 30 minutes. All experimental sessions were conducted between 9 a.m. and 12 noon. Due to the variability and uniqueness of each horse's baseline responding rates (Table 1), the data is expressed as a percentage of control. This allows data from horses that responded at rates several fold different in absolute values to be meaningfully compared. Horses injected with saline produced no change in responding rates during their experimental periods when compared to non-injection sessions and are expressed as 100 % of control. Drug data points were compared using the student's t test with .05 set as the significance level.

RESULTS

The results obtained in this study are presented in Fig 2. As expected, both xylazine and detomidine decreased responding rates of the horses when tested 1 hr after administation with detomidine clearly producing a more dramatic effect (12% of control). In addition, 24 hrs after this dose of detomidine the responding rates were still significantly less than baseline levels (79% of control,$p<.05$) . At 48, 72 and 96 hrs after administration of these agents, all responding rates were within 5% of the saline control levels.

DISCUSSION

Behavioral pharmacology and toxicology are independent disciplines that can answer many important questions concerning subtle and long-term effects of drugs (Seiden and Dykstra, 1977 ). While operant conditioning has been widely used in lab animals for many years, very few studies have been performed using the horse as the subject animal. However, good results have been obtained in the few reported studies (Shults et al, 1982, Meyers and Mesker, 1960 ). It would appear that this type of behavior monitoring can be a valuable method in equine pharmacology to provide additional information when compared to traditional methods (Tobin and Combie, 1982 ). The horse can easily be trained to respond for an appropriate reinforcer. Once trained, the horse will develop baseline response rates that are remarkably stable and unique to the individual horse. Rate of behavior is a very sensitive indicator of drug effects that are not readily detectable by clinical observation.

Accurate and objective measurements of subtle effects of drugs on the central nervous system in the horse is important in attempting to produce guidelines for their use. It is especially important to correlate their effects when their blood concentrations are very low to evaluate their abuse potentials when used in a subclinical manner. Pharmacological studies conducted in Finland and the United States indicate that detomidine has a dose-response curve with a low range of doses that would not be easily detected analytically (Jochle

and Hamm, 1986,and Salonen, 1986 ). It appears that detomidine and xylazine because of their relatively short duration of action do not have the same time course for abuse potential as reserpine in performance horses. However, the data presented here suggests that residual effects of detomidine can have a depressive effect on CNS mediated rates of behavior for up to 24 hrs. The use of VI responding rates should be quite valuable in determining a dose-response curve of subtle effects of detomidine as well as other drugs suspected of having residual properties. Because of the stable and relatively high base-line rates of behavior demonstrated by horses trained to this system, this method appears to be well suited for studies of depressant drugs. Detomidine, like many drugs used in equine medicine, have a time course of action measured in hours rather than days. Protocols will have to be modified to accurately determine when their residual effects have completely dissipated. Operant conditioned horse can be incorporated into these protocols to provide valuable information concerning the time course of drugs used in veterinary medicine.

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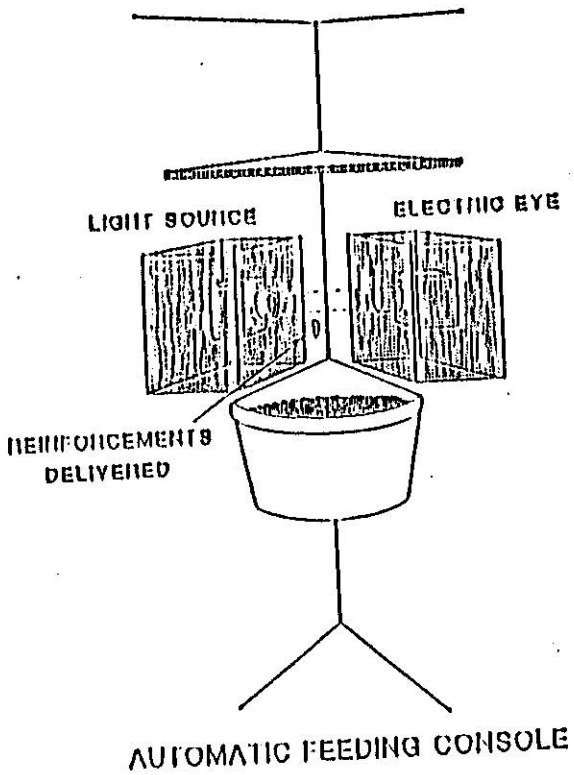
FIGURE 1.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