Pharmacologic Treatment of Equine Self-Mutilation Syndrome

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ABSTRACT

The effects of drugs that either stimulate or inhibit central opioid, dopamine, norepinephrine, and serotonin neurotransmitter systems were examined in horses demonstrating signs of equine self-mutilation syndrome (ESMS), a condition similar to Tourette's syndrome in humans. Eight flank-biting horses with ESMS were recruited for the study. A series of drugs selected for their activity on the aforementioned neurotransmitter systems were administered to the horses in a saline-controlled behavioral study. Specific behaviors associated with the syndrome were videotaped for 4 hours following administration of drug or saline. Behaviors recorded hourly during each phase of the study were compared with those of a composite saline control baseline to determine whether there were significant differences among the treatments. Acepromazine, a dopamine blocker, produced a significant reduction in the primary ESMS behaviors of self-mutilative attempts and hemiballismus. Detomidine, an α-2 antagonist, also produced a significant ($P < .05$) reduction in these behaviors, as did the opioid-receptor antagonist naltrexone and the serotonin agonist buspirone. These findings provide new information on the neurophysiological basis of ESMS and suggest further parallels with Tourette's syndrome.

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INTRODUCTION

First described as self-directed aggression,[1,2] equine self-mutilation syndrome (ESMS) or flank-biting has been further delineated as an equine equivalent of Tourette's syndrome (TS).[3] The prevalence of ESMS in the equine population is unknown; however, 0.7% of geldings and 1.9% of stallions from a survey of more than 700 horses in Canada were reported to be affected (U. A. Leuscher and D. B. McKeown, unpublished data). Behavioral parallels between ESMS and TS include head and neck motor tics, hemiballismus (constant, undirected, purposeless striking out with either a forelimb or hindlimb), preoccupation with environmental boundaries, and occasional bizarre vocalizations. Other similarities include juvenile onset, male predilection, familial tendency, an unrelenting course, exacerbation by stress, amelioration by absorbing activities, unimpaired performance, and occasional precipitation by trauma.[4–7]

Endorphins and enkephalins have been suggested as the predominant group of opioids involved in the pathophysiology of the

TS.[8] Opioids may have dual modulatory effects on tic expression, although low doses of opioid antagonists often reduce tic frequency.[6] Dopamine pathways are also involved in the pathogenesis of TS, as evidenced by the palliative effects of both dopamine antagonists (e.g., haloperidol) and agonists (e.g., apomorphine and pergolide).[8–11] Additionally, norepinephrine appears to be to be involved in the pathobiology of TS because norepinephrine levels in cerebrospinal fluid are 55% higher in patients with TS than in healthy controls, and clonidine suppresses TS tics.[12,13] Finally, the fact that selective serotonin reuptake inhibitors are drugs of choice in TS suggests the involvement of serotonergic mechanisms.[7]

The only evidence of a role for any of these neurotransmitter systems in ESMS is from a clinical survey in which two horses with ESMS reportedly responded to therapy with a dopamine antagonist and a case report describing the suppression of ESMS tics with nalmefene, an opioid antagonist.[3,4]

The present study was conducted to investigate neurobiologic similarities between ESMS and TS. The effects of drugs that either stimulate or inhibit central opioid, dopamine, noradrenergic, and serotonin pathways on ESMS were studied. Individual drugs were selected based on familiarity with their use in horses and their principal mechanism of action.

MATERIALS AND METHODS

Horses

Eight horses identified as flank-biters were admitted to the Large Animal Hospital of Tufts University School of Veterinary Medicine for clinical evaluation and possible enrollment in a behavioral study approved by the Institutional Animal Care and Use Committee (Table 1). A signed owner consent was obtained for each horse participating in the study. Each horse was given a thorough physical evaluation, including a general medical examination, gastric endoscopy, retinal examination, reproductive assessment (testicular palpation and measurement or ovarian and uterine examination by rectal palpation), and dermatologic examination (by direct visual inspection and microscopic examination of skin scrapings) to eliminate possible medical causes for the abnormal behavior. Additionally, a blood sample was collected by venipuncture from each horse for a complete blood count and chemistry profile analysis. Finally, at least 48 hours after admission to the clinic, horses were observed and then videotaped for 4 hours to confirm that each was exhibiting behavior characteristic of ESMS. Two horses (M and MD) had to be blanketed at all times to prevent them from injuring themselves during their intense self-mutilation episodes. One horse (B), a high-intensity cribber, was always equipped with a cribbing collar.

Table 1. Identification of Horses Presenting with Equine Self-Mutilation Syndrome

Horse ID	Sex	Breed	Age (yr)
PST	Stallion	Arabian	7
M	Stallion	Arabian	15
DR	Gelding	Quarter horse	13
RV	Stallion	Arabian	12
MD	Stallion	Paint	3
NP	Mare	Thoroughbred	2
B	Gelding	Oldenburg	4
PB	Mare	Standardbred	2

ESMS was diagnosed based on the observation of self-mutilative attempts or actual flank-biting; hemiballismus; excessive head-tossing; bizarre, unsolicited vocalization; preoccupation with the periphery of the stall; and constant sniffing, especially of manure. Sudden explosive bouts of self mutilation or flank-biting associated with any of other characteristic signs (and the absence of any medical explanation for the behavior) was considered diagnostic of ESMS.

Treatments

Drugs evaluated included detomidine, naltrexone, morphine, acepromazine, cocaine, apomorphine, amphetamine, clomipramine, haloperidol, and buspirone. Dosages, routes of administration, and mechanisms of action

Table 2. Dosages, Routes of Administration, and Mechanisms of Action for Drugs Administered to Horses with Equine Self-Mutilation Syndrome

Drug	Dosage (mg/kg)	Route	Neurotransmitter System Targeted
Acepromazine	0.02	IV	Dopamine antagonist
Amphetamine	0.4	IV	Increases dopaminergic and noradrenergic activity
Apomorphine	0.06	IV	Increases dopaminergic activity
Buspirone	0.5 (2 hours prior to taping)	PO	Partial agonist for serotonin receptors
Clomipramine	1–2	PO daily for 3 wk	Serotonergic enhancement
Cocaine	0.75	IV	Increases dopaminergic, noradrenergic, and serotonergic activity
Detomidine	0.02	IV	Inhibition of norepineprine release
Haloperidol	0.5	IV	Dopamine antagonist
Morphine	Escalating doses: 0.05, 0.1, 0.2, 0.4 at 30-min. intervals	IV	Opioid agonist
Naltrexone	0.5–1.0	IV	Opioid antagonist

of each drug are shown in Table 2. On treatment days, one drug was administered via IV catheter, and behaviors were monitored and recorded in the same manner as for the control periods. Two drugs (buspirone and clomipramine) were administered orally in a small quantity of molasses-flavored grain. The sequence of treatments is shown in Table 3.

Evaluations

The horses were observed in a padded stall equipped with a wall-mounted video camera wired to a television and videocassette recorder. Behavior for each horse was monitored for five 4-hour observation periods following IV injection of saline at approximately 4- to 5-day intervals during the first 3 weeks of each horse's 6-week stay in the hospital. Control measurements were recorded before and between drug treatments, with the exception of clomipramine.

In most cases, horses were videotaped during the 4-hour period immediately following a drug's administration. Two exceptions were for clomipramine and apomorphine. Because of its slow onset of action, clomipramine was administered daily for 3 weeks, and the 4-hour videotaping was done only at the end of this treatment period.[14] Horses treated with apomorphine were videotaped for only 2 hours after treatment because apomorphine has a transitory effect in horses.

Based on what is known about each drug's pharmacodynamics and pharmacokinetics, at least 24 hours was allowed for drugs to clear before each control-period measurement. Four relevant, easily quantifiable behaviors (self mutilation attempts, spontaneous kicks, head tosses, and vocalizations) were recorded for each horse during each observation period. The results, expressed as events per hour, were used as baseline data. Videotaped behaviors were always scored by the same observer in this open (non-blinded) clinical study.

Statistical Analysis

Data were entered into a commercially available software package (SPSS), and descriptive statistics were generated. Each horse served as its own control. To obtain the most representative control frequency of ESMS behavior for each horse, the frequency of each of the four monitored behaviors

was averaged for each hour for all control periods combined. Since the data were not normally distributed and the sample size was small, a nonparametric test for paired data (Wilcoxon signed rank test) was used to compare the frequency of behaviors at each time period in the control period after each drug was administered. Significance was determined at $P \leq .05$ level.

RESULTS

None of the horses had any clinically relevant medical findings on physical, hematologic, or biochemical analysis. Based on the failure to identify any medical cause for the behavior exhibited by the horses and the presence of characteristic clinical signs, ESMS was the confirmed diagnosis for each horse enrolled in the study.

Gross inspection of the results indicated that of the four behaviors that were easily monitored, only self-mutilative attempts (including flank-biting) and hemiballismus occurred with sufficient frequency for meaningful analysis. Each of the remaining behaviors occurred less than three times per hour. The relative frequency of self-mutilative attempts and hemiballismus varied among the horses during the control periods, and neither activity was more representative than the other of the syndrome. Thus, to obtain a single stable indicator of ESMS behavior, the numbers of self-mutilative attempts and kicks were summed for each horse at each time. The total hourly frequency of these signs at baseline was used as the criterion to evaluate the response to drug treatments. Because horses were affected to different degrees, median frequencies of the behaviors were used, rather than the mean. The same control values were used for comparison in all trials (Figure 1).

Manipulation of the Dopaminergic System

Dopamine Blockade

Acepromazine produced a significant ($P < .05$) reduction in the frequency of signs for 3 hours following IV injection. However, it also produced generalized sedation and an

Table 3. Sequence of Treatments Administered to Horses with Equine Self-Mutilation Syndrome

Sequence of Drugs Given to Each Horse						
PST	**M**	**DR**	**RV**	**MD**	**NP**	**B**	**PB**
Detomidine	Detomidine	Detomidine	Detomidine	Detomidine	Detomidine	Detomidine	Detomidine
Naltrexone	Naltrexone	Naltrexone	Naltrexone	Naltrexone	Naltrexone	Morphine	Morphine
Morphine	Morphine	Morphine	Morphine	Morphine	Morphine	Naltrexone	Naltrexone
Acepromazine	Cocaine	Acepromazine	Cocaine	Acepromazine	Acepromazine	Haloperidol	Acepromazine
Cocaine	Acepromazine	Cocaine	Acepromazine	Haloperidol	Cocaine	Amphetamine	Buspirone
Apomorphine	Apomorphine	Apomorphine	Apomorphine	Apomorphine	Buspirone	Buspirone	Amphetamine
Amphetamine	Amphetamine	Amphetamine	Amphetamine	Amphetamine	Haloperidol	Acepromazine	Haloperidol
Clomipramine	Buspirone	Buspirone	Haloperidol	Cocaine	Apomorphine	Cocaine	Cocaine
No treatment	Clomipramine	No treatment	Clomipramine	Buspirone	Amphetamine	Apomorphine	Apomorphine
Haloperidol	Haloperidol	No treatment	Buspirone	Clomipramine	Clomipramine	No treatment	Clomipramine

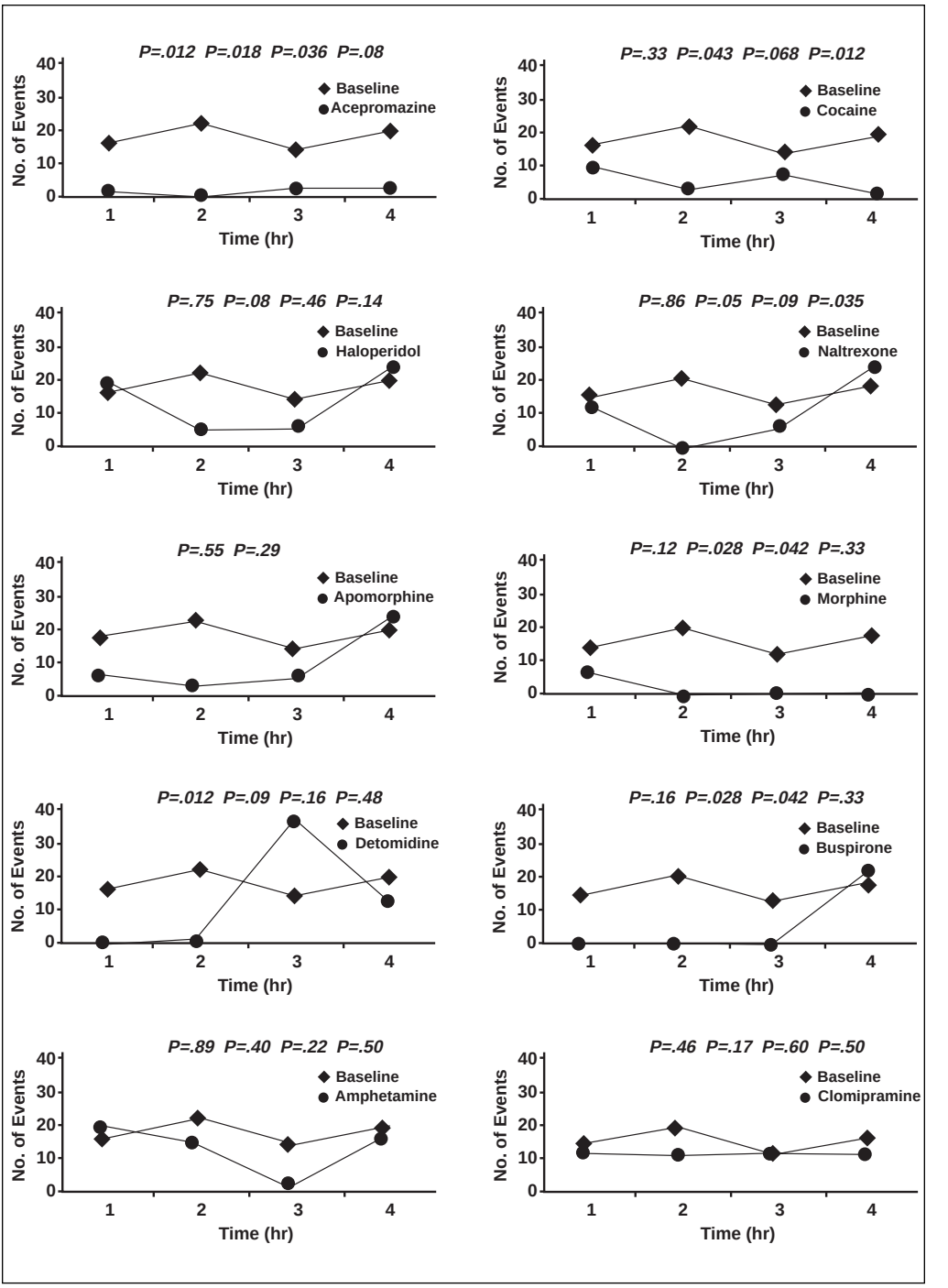

Figure 1. The median number of kicks and self-mutilating attempts for horses before and after drug administration. *P* values refer to comparisons of treatment versus control values by the Wilcoxon signed rank test.

associated decrease in all motor activities. Haloperidol also produced sedation, which was most pronounced during the first 2 hours following administration. The apparent reduction in ESMS behavior following haloperidol approached significance during the second hour after treatment (Figure 1).

Dopamine Activation

Ten to 15 minutes after IV injection of apomorphine, the horses began to exhibit loud, stertorous breathing and circling in the stall. Apomorphine reduced the frequency of signs of ESMS, but the reduction did not reach the level of significance when the hourly rate of ESMS behavior was computed and compared with that for the control measurements.

Manipulation of Catecholamines

Inhibition of Norepinephrine Release

Detomidine, an α-2 blocker, produced a significant ($P < .05$) reduction in the ESMS score for the first hour after IV injection. The reduction approached significance during the second hour. As with acepromazine and apomorphine, the reduction in the frequency of ESMS behavior was associated with marked sedation (Figure 1).

Stimulation of Norepinephrine/Dopamine Systems

Amphetamine and cocaine stimulate norepinephrine release and increase activity in dopamine systems. Amphetamine did not significantly alter the frequency of ESMS events during the 4-hour test period. Treated horses appeared anxious and spent most of the time walking around the stall. They became noticeably engaged in head bobbing and blinking. Cocaine produced a significant ($P < .05$) reduction in ESMS activity in the second and fourth hours following injection. The reduction approached significance during the third hour after drug administration. Some horses became extremely tense and "frozen" in posture and showed constant twitching of their ears following administration of cocaine. Others engaged in head bowing, pawing, or biting at the padding inside the stall (Figure 1).

Manipulation of the Opioid System

Opioid Blockade

Following an initial period of increased activity lasting approximately 15 minutes, horses treated with naltrexone showed a significant ($P < .05$) reduction in the frequency of ESMS events in the second and fourth hours following treatment. There was a reduction in frequency of activities that approached significance during the third hour. During the entire period after treatment, the horses showed mild sedation similar to that produced by nalmefene (Figure 1).[15]

Opioid Activation

Morphine produced a significant ($P < .05$) decrease in ESMS behavior in the second and third hours following IV injection. Increased motor activity was apparent toward the end of the first hour, possibly contributing to the decrease in ESMS behavior (Figure 1).

Manipulation of the Serotonergic System

Buspirone, a serotonin agonist, produced a significant ($P < .05$) decrease in ESMS activities in the second hour following oral administration. The horses appeared alert during the entire observation period, although they exhibited considerable pacing in the stall. Clomipramine, administered daily (PO) for 3 weeks did not provide any observable affect on ESMS behavior in these horses.

DISCUSSION

The results support the contention that ESMS resembles human TS.[3] The decrease in ESMS–related behavior produced by acepromazine indicates that dopamine plays a facilitatory role in ESMS as it does in TS.[8,9,17,18] The duration of the effect of acepromazine was relatively prolonged, as would be expected from a drug with a half-life of 50 to 150 minutes and a prolonged pharmcodynamic action in horses.[19] Also, the reduction in the frequency of ESMS behavior observed for apomorphine, although failing to achieve significance, is similar to what has been reported for this

drug in the treatment of TS.[17] The lack of significance may be attributable to apomorphine's short (<30 minutes) action in horses after IV injection.[15] It is also possible that 1-hour time blocks are too long for quantitation of clinical response in this study. The apparent paradoxical response to dopamine receptor blockade and agonism in ESMS and TS may be a dose-related phenomenon, the result of selective presynaptic striatal effects of dopamine agonists, or due to direct/indirect effects on sensory gating or motor-output channels via postsynaptic, cortical dopamine receptors.[12]

The observation of a significant ($P <$ .05) decrease in ESMS behavior with detomidine, an α-2 agonist, is in accord with to the response of humans with TS to clonidine, a drug with a similar action.[20,21] This finding suggests a role for norepinephrine in facilitating both conditions. The duration of detomidine's clinical effect was in agreement with what is known about its pharmacokinetics. Detomidine has a half-life of 1.78 hours following IV injection in horses.[22]

A pronounced decrease in ESMS behavior was produced by the opioid antagonist, naltrexone. This finding is in agreement with an earlier report for another narcotic antagonist (nalmefene) used as a treatment for ESMS.[4] The results are also similar to findings reported for humans suffering from TS.[23]

Both morphine and naltrexone caused a significant ($P < .05$) decrease in ESMS behavior. The decreases observed after morphine may have been secondary to increased motor activity, or they could be explained by repletion of an otherwise deficient reward system, as hypothesized for various impulsive, addictive, and compulsive behaviors in humans.[24] The response to these drugs might also be explained by their common action as N-methyl-D-aspartate–receptor antagonists.[25] Morphine's effects only became apparent toward the end of the first hour following administration of an "analgesic dose" (0.1 mg/kg) at the 30-minute mark. Considering morphine's half-life in horses (87.9 minutes) and with increasing doses of morphine being administered to the horses every 30 minutes, the sustained (4-hour period) clinical effects were an expected finding.[26]

The suppression of ESMS activities with buspirone suggests a role for serotonergic modulation of the behavior. With TS, drugs that activate serotonergic systems have an inhibitory effect on symptoms.[9,27] Buspirone appeared to have 2 to 3 hours of activity at the dosage used in this study (0.5 mg/kg). This duration of action is consistent with earlier unpublished observations and with published data on the pharmacokinetics of buspirone in horses.[28]

Curiously, clomipramine, a preferential serotonin reuptake blocker, did not produce any significant effect on ESMS behavior in the horses in this study. The lack of effect may have been related to the short duration of administration (3 weeks) or to the relatively low dose employed. In humans, serotonin reuptake inhibitors are drugs of choice for the treatment of many aspects of TS, although tics may be better controlled with dopamine antagonists.[9]

Cocaine produced a significant ($P < .05$) decrease in ESMS behavior in these horses, which was not an expected finding, considering that cocaine may induce tics in humans with TS.[29] However, as with morphine, the ancillary actions of cocaine may have overshadowed its primary pharmacologic effect. Additionally, the actions of cocaine are difficult to identify because it blocks the reuptake of several monoamines, and resulting stimulation of presynaptic receptors for these neurotransmitters may cause decreased motor activity. Thus, cocaine's effects may be somewhat ambivalent and perhaps species and dose dependent. Amphetamine produced no significant decrease in ESMS behavior, perhaps because the behavioral effects were overshadowed by the horses' continuous walking. In humans with TS, stimulants tend to exacerbate the symptoms.[30]

The present study indicates that some manipulations of catecholaminergic, dopaminergic, and opioidergic systems in horses with

ESMS alter the frequency of expression of the behavioral signs. These neurotransmitter systems are also involved in the symptomatology of TS in humans. Alterations in the behavior of horses with ESMS produced by agonism or antagonism of these neurotransmitter systems were generally in the same direction as would be anticipated with their application for humans with TS. Although ESMS has some face and predictive validity as a model of human TS, the full construct of this putative model remains to be validated.

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