

Imipramine-Induced Erection, Masturbation, and Ejaculation in Male Horses

S. M. McDONNELL, M. C. GARCIA, R. M. KENNEY

*University of Pennsylvania, School of Veterinary Medicine
Section of Reproductive Studies, New Bolton Center, Kennett Square, PA 19348*

AND

K. N. VAN ARSDALEN

*Department of Urology, Hospital of the University of Pennsylvania
3400 Spruce Street, Philadelphia, PA 19104*

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McDONNELL, S. M., M. C. GARCIA, R. M. KENNEY AND K. N. VAN ARSDALEN. *Imipramine-induced erection, masturbation, and ejaculation in male horses*. PHARMACOL BIOCHEM BEHAV 27(1) 187-191, 1987.—Imipramine hydrochloride was administered to five male horses (400-500 kg b.wt.): one inexperienced young stallion, two mature normal breeding stallions, one 5-year-old stallion with erection and ejaculatory dysfunction, and one long-term castrated male horse. Oral imipramine treatment (100 to 600 mg, twice daily) led to frequent erection and masturbation while at rest in the stall in a nonsexual context. Intravenous imipramine treatment over a range of doses (50 to 1000 mg) similarly induced erection and masturbation in all animals. Erection typically occurred within 10 minutes after injection, and the erection and masturbation continued intermittently for 1 to 2 hours. These erections proceeded as during sexual excitement to a normal firmness and eventual engorgement of the glans penis. Two stallions ejaculated while masturbating. Mild ataxia and drowsiness appeared at the higher doses, but the animals remained responsive to auditory, visual, and tactile stimuli. Erection and masturbation were often interrupted by activities about the barn or the approach of the handler, suggesting cortical inhibitory control of the erection. When tested in a sexual context immediately following IV treatment (500 mg), the two mature breeding stallions bred normally. The 5-year-old stallion, which had not ejaculated over several months of breeding attempts, spontaneously ejaculated following IV imipramine treatment. Subsequently, this stallion has ejaculated during copulation while on low dose oral (100 mg, twice daily) imipramine treatment. Plasma total androgens increased during treatment in these stallions. The long-term castrate showed erection and masturbation following IV imipramine treatment, suggesting that the effect of imipramine is not testosterone dependent.

Stallion	Sexual behavior	Imipramine	Erection	Ejaculation	Tricyclic antidepressant	Yawning
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HORSE stallions, like primates, are single-mount, multiple thrust ejaculators. Erection of the musculocavernous penis must occur before intromission can be achieved. The penis of the stallion at rest lies withdrawn into the preputial sheath within the inguinal region (Fig. 1a). It protrudes from the sheath for urination and during sexual activity. For urination, the penis usually protrudes less than full length and remains flaccid (Fig. 1c). During sexual excitement, the penis reaches its full length as erection proceeds (Fig. 1d and e) via engorgement of the corpora cavernosa and spongiosum. During copulation the glans penis enlarges up to four times its normal diameter as the corpus spongiosum engorges [1]. Outside the mating context, stallions also frequently exhibit full erection, contraction of ischiocavernosus muscles resulting in rhythmic bouncing of the penis against the belly (Fig. 1f), and occasionally ejaculation [12]. Accompanying skeletal movements, including variations of pelvic thrusting, suggest a goal directed self stimulation of the glans penis.

Accordingly, this behavioral sequence is viewed as masturbation. Among domestic horses, masturbation is commonly observed in stabled stallions, but also occurs in stallions at pasture with other horses (McDonnell, personal observations). Free-running feral and wild stallions, both harem [6] and bachelor (Berger, personal communication, 1987) band stallions, also exhibit erection and masturbation in apparently nonsexual contexts.

The dibenzazepines imipramine and clomipramine, used widely in humans as antidepressants, are known to influence erection and ejaculation [2, 3, 11]. Both disturbance and facilitation of sexual response have been reported. In the case of facilitatory effects, it has been difficult to determine whether improved erection and ejaculation are specific drug effects or the consequence of the attenuation of depression. Treatment of depression with clomipramine has been associated with spontaneous orgasm, including ejaculation in men [9]. In doses about one quarter of those used for treat-

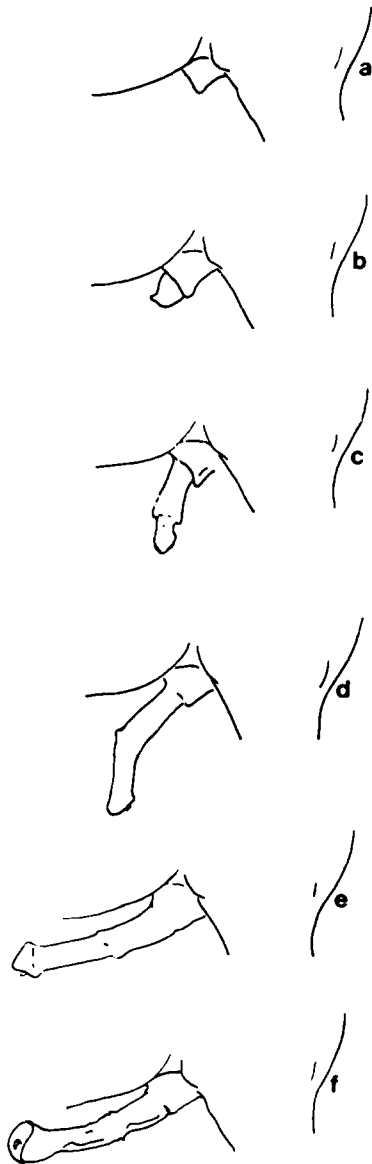


FIG. 1. Penis positions in the stallion, at rest (a), and during penis drop (b,c), erection (d,e), and masturbation (f).

ment of depression, imipramine is used to treat ejaculatory dysfunction in non-depressed men (Van Arsdalen, unpublished).

Erection and ejaculatory dysfunction are common fertility limiting problems in domestic stallions. These problems may occur in association with inadequate sexual interest and arousal, but also occur in conjunction with otherwise normal, even vigorous, precopulatory and copulatory responses. Limited success in facilitating erection and ejaculation has been achieved with a number of neuromyotrophic agents [8].

Described below are trials conducted to evaluate the effects of imipramine on erection and ejaculation in the horse (*Equus caballus*) stallion. The work was done in three stages. First, during a preliminary single-subject imipramine

TABLE 1
SEXUAL RESPONSES OBSERVED DURING 60 MINUTES FOLLOWING IV IMIPRAMINE TREATMENT (NONSEXUAL CONTEXT)

Dose	Latency (min) to:	
	Erection	Masturbation
a. Young Sexually Naive Stallion		
600 mg	2	3
600 mg	5	5
600 mg	4	4
600 mg	9	40
600 mg	5	5
1000 mg	2	2
1000 mg	5	30
b. Mature Stallion A		
50 mg	—	—
200 mg	8	8
300 mg	30	40
500 mg	5	5
800 mg	4	4*
Mature Stallion B		
50 mg	—	—
200 mg	—	—
300 mg	30	30
500 mg	6	7
800 mg	10	10
c. Stallion With Erection and Ejaculatory Dysfunction		
200 mg	30	—
250 mg	30	—
350 mg	21	21†
350 mg	28	28‡
350 mg	10	10
350 mg	3	3
350 mg	7	7
350 mg	5	5
400 mg	8	8
500 mg	9	9
500 mg	4	5
d. Long-Term Gelding		
300 mg	—	—
300 mg	35	—
500 mg	8	—
500 mg	3	4
800 mg	30	—
800 mg	10	13

*Ejaculation at 7 min.

†Ejaculation at 23 min.

‡Ejaculation at 12 min.

toxicity trial, a stallion appeared to exhibit increased frequency of erection and masturbation while on a gradually increasing oral dose, as well as erection and masturbation immediately following IV injection of imipramine. Subsequently, a series of trials were conducted to study these effects on behavior in two mature breeding stallions and a stallion with erection and ejaculatory dysfunction. Finally, the effects of imipramine on erection and masturbation were evaluated in a mature, long-term castrate (gelding). This

work was done during March, April, and May of 1986, months during the beginning of the natural breeding season for the horse.

METHOD AND RESULTS

Preliminary Study

As a preliminary evaluation of the effects of imipramine treatment in the horse, a single horse was given an oral treatment of imipramine hydrochloride. The subject was a two-year-old sexually naive Thoroughbred stallion obtained from a local breeding farm. The stallion was housed under standard farm conditions in a 4×4m stall with daily exercise in a 1 acre paddock, and was maintained on hay and grain given twice daily and fresh water ad lib. The subject was placed on gradually increasing daily doses of imipramine hydrochloride tablets mixed in with the grain ration (200 mg, orally, twice daily for 7 days, followed by 300 mg, twice daily for 4 days, and 600 mg, twice daily for 7 days; Rugby Laboratories, Rockville Center, Long Island, NY). Following this regimen, the horse received 600 mg, orally, twice daily for 7 days during which IV injections of imipramine hydrochloride (Sigma Chemicals, St. Louis, MO) dissolved in sterile water (at 100 mg/ml) were also given (600 mg for 5 days, followed by 1000 mg for 2 days). Jugular blood samples were collected before treatments began and at 1 to 2 day intervals during treatment to monitor hemogram, BUN, AST, plasma androgens, T₃, T₄, and cortisol. (All assays adapted for equine and conducted by Diagnostic Endocrine and Clinical Pathology Laboratories, New Bolton Center, Kennett Square, PA 19348.) Cardiac and respiratory rates were monitored daily. In addition, general attitude and activity were noted twice daily. Following IV administration, the stallion was observed continuously for 1 to 2 hours. Activity, attitude, as well as cardiac and respiratory rates were recorded.

Oral treatment led to no observable change in general activity, attitude, or appetite. Intravenous treatment led to a cluster of specific behavioral responses within a period of 1 to 2 hours following injection. During the first 10 to 20 minutes following each administration, the stallion exhibited frequent tail lifts, defecation, occasional nibbling at straw, abdominal twitching, mild ataxia and unwillingness to move. This was followed by a quiet, resting posture with lowered head and drowsy expression, but with normal responsiveness to environmental visual and auditory stimuli. The animal remained normally attentive to approaching handlers and consumed grain or hay in a normal fashion when it was presented. General attitude and activity returned to normal within 3 to 4 hours after each injection.

During oral treatment, the stallion showed frequent erection and masturbation in the stall, as noted by experienced stallion caretakers (blind to the treatment) during routine stall checks (hourly, 24 hr/day). Unlike normal stallions which may be observed with full erection or masturbating once or twice weekly, this stallion was rarely found without an erection or masturbation during the hourly observations. Erection and masturbation were observed within minutes after each IV injection and were associated with the drowsy posture. This behavior, summarized in Table 1a, occurred within the first 10 minutes, and continued intermittently for 1 to 2 hours after each injection. The penis drop and erection proceeded as during normal sexual arousal, except that on two occasions the stallion urinated during the partial penis drop before erection commenced. With masturbation, the glans penis became engorged and watery fluid dripped

from the urethra. As with most stallions that are occasionally found masturbating in their stall, erection and masturbation were readily disrupted by activity in the barn, especially the approach of a handler.

Cardiac rate, respiratory rate, hemograms, BUN, and AST remained clinically normal throughout oral and IV treatment. Plasma total androgens increased with treatment. Moderate increases (0.48 to 0.96 ng/ml) during the initial 2 weeks of oral treatment were followed by marked further increase coincident with IV treatment. Plasma total androgens increased from 0.96 to 1.71 ng/ml within 5 hours of the first injection. Levels remained above 1.80 ng/ml during the week of IV treatments, and returned to 0.97 ng/ml one week later. It is possible that a portion of this increase may represent the characteristic seasonal increase in androgens (approximately 25 to 50% over 3–4 months from winter low to spring high [4,7]), however such acute marked increases suggest direct response to imipramine. Plasma cortisol levels dropped to very low levels during oral treatment.

Two Mature Sexually Experienced Stallions

The effects of IV injection of imipramine on erection and masturbation were studied in two mature, sexually experienced stallions. These stallions (one 10-year-old Standardbred and one 9-year-old Thoroughbred) had been maintained under standard farm conditions at a veterinary teaching hospital for several years for the purpose of demonstrating semen collection and evaluation. Each stallion received 5 different imipramine dose level trials (50, 200, 300, 500, and 800 mg, in random order) and 5 corresponding equivalent volume vehicle control trials. This was accomplished by conducting two sets of trials for each dose level at 1–3 day intervals over a period of three weeks. On the occasion of each set, one of the stallions received imipramine and the other vehicle only. The trials were conducted in each stallion's stall, with no mares nearby. A single observer, blind to treatment, stood within sight of both stallions, recording the behavioral response as described above. Blood samples and clinical observations were conducted as described above. In addition, each stallion was given a trial in which an IV injection of 500 mg was administered 2 minutes before the stallion was taken to the breeding area for collection of semen. Results were compared with the known performance of these stallions in similar situations. Several weeks later one of these stallions was placed on long term oral treatment (100 mg, twice daily for 6 weeks).

In all control trials, no full erection or masturbation occurred. As shown in Table 1b, erection and masturbation reliably followed IV imipramine doses of 200 mg or greater in one stallion and 300 mg or greater in the other. Penis drop occurred after all imipramine injections. Ejaculation during masturbation was observed in one stallion. Abdominal muscle twitches, frequent tail lifting, defecation, nibbling of straw, and the drowsy posture similar to that described above, were also observed in these animals. As with the younger novice stallion, the erection and masturbation responses usually occurred within 10 minutes after injection and continued intermittently for at least 1 hour.

Sexual arousal and response of these two stallions remained normal (full erection, mount, and ejaculation within 3 minutes of presentation to the stimulus mare) during the collection of semen immediately following imipramine injection. Sexual behavior during routine semen collections also remained normal in the stallion placed on long-term oral treatment.

Plasma testosterone levels approximately 6 hours after IV

injections were high normal (1.2 to 2.10 ng/ml; recent baseline values had ranged from 0.80 to 1.05 ng/ml for these stallions). Cortisol levels, BUN, AST, and hemograms were normal throughout these treatments.

Stallion With Erection and Ejaculatory Dysfunction

A 5-year-old Standardbred stallion with spontaneous sexual dysfunction was studied. This successful, retired racing stallion had failed to ejaculate despite intermittent breeding attempts over a two year period. Initially, this stallion was timid and slow to become aroused. Eventually, the animal showed near-normal sexual interest and arousal, with willingness to mount, insert, and thrust. Although near-normal, erection was occasionally not firm enough to achieve insertion and frequently subsided within a few seconds after intromission. Attempted therapies during the two years included beta blockers, oxytocin, diazepam, and ephedrine. This animal was placed on oral imipramine hydrochloride (100 mg, twice daily). In addition, IV treatments at various dose levels were given 3 to 4 times weekly as described above, over a 6 week period. For several weeks before and during treatment, the stallion was presented 3 to 4 times weekly to a mare for breeding.

Oral treatment led to increased erection and masturbation in the stall. As shown in Table 1c, IV injection reliably produced erection and masturbation. Ejaculation occurred on two occasions following a 350 mg injection. In addition to tail lifts, defecation, abdominal twitches, and drowsiness seen in the other stallions, this stallion reliably showed bouts of yawning-like behavior while in the drowsy state following IV imipramine treatment. Coincidentally, similar peculiar yawning bouts had been noted in this stallion during the many lengthy unsuccessful breeding sessions over previous months.

Plasma testosterone increased with imipramine treatment, while plasma cortisol decreased. BUN, AST, other plasma hormones, and hemograms remained within normal ranges.

This stallion subsequently ejaculated during copulation while on oral treatment (100 mg, twice daily). A pregnancy resulted. No adverse effects were detected during or following 180 days of oral treatment.

Long-Term Gelding

To test whether the erection and masturbation response seen in the intact stallions may be related to increased testosterone, a 19-year-old gelding was given several IV doses (300, 500, and 800 mg—each on two occasions) of imipramine hydrochloride at 1–2 day intervals over a period of 2 weeks as described for the mature stallions. Equivalent volume vehicle control trials were randomly interspersed between imipramine trials. The behavioral response, measured as described above, was similar to that of the intact stallions studied. No erection or masturbation occurred following control treatments. Erection and masturbation responses following imipramine treatment are shown in Table 1d. Erection followed each dose, and masturbation occurred during two of the six treatment trials. BUN, AST, and hemograms remained clinically normal. Plasma total androgens and cortisol did not change with treatment.

DISCUSSION

Erection and masturbation reliably followed imipramine

treatment in these male horses. Ejaculation was observed during masturbation in two stallions. The behavioral response of the castrated animal was similar to that of the four intact stallions. These sexual responses occurred in the absence of a stimulus female, and closely resembled spontaneous erection and masturbation frequently observed in stallions.

Although erection and masturbation consistently followed imipramine treatment, neither appeared to be an uncontrollable response. There were clear signs of cortically mediated inhibition of erection and masturbation. The imipramine-induced erection and masturbation responses were distinct from penis drop and occasional "penile paralysis" associated with phenothiazine tranquilization in horses, in which the penis is extended, but flaccid, with no resulting masturbation and little or no flaring of the glans penis. The response to phenothiazines has been interpreted as a result of compromised neuromuscular mechanism for retraction of the penis, followed in some cases by pooling and thrombi.

In contrast to most previous reports of work in humans and laboratory species [10], our results indicate consistently positive effects of imipramine on sexual behavior of the horse. Most trials in the stall resulted in erection and masturbation. In a breeding situation, the mature stallions showed no apparent adverse effect of imipramine on erection or ejaculation. Long-term oral treatment had no noticeable deleterious effects on erection or ejaculation. In the stallion with spontaneous erection and ejaculation problems, treatment appeared to have a positive effect.

Our results suggest facilitatory effects of imipramine on erection and ejaculation independent of generally improved mental state or initial sexual dysfunction. These stallions were not depressed and exhibited normal sexual behavior before and during treatment. The positive effects on these sexual responses were consistent over a range of doses. Although the central and peripheral mechanisms involved in male sexual arousal, erection, and ejaculation are not clearly understood, there are several systems involved through which these imipramine effects might be mediated. Centrally, imipramine differentially affects norepinephrine, dopamine, and serotonin systems, all known to influence sexual behavior. In addition, there are several known effects of imipramine on autonomic nervous system function that might explain effects on erection and ejaculation [14]. Principal among these are inhibition of norepinephrine re-uptake and mildly anticholinergic properties.

Although testosterone increased with the oral/IV schedule of treatment in the intact horses, the erection and masturbation following imipramine treatment in the castrate suggests that these effects are not androgen dependent.

The yawning behavior of the clinical case stallion seemed peculiar both in the breeding environment before treatment and in the stall following IV treatment. Horses do yawn in association with a drowsy state [13], but yawning has apparently not been noted in a sexual situation, including during masturbation. Unlike in some primates [5], yawning in the horse is not known to be a sexually dimorphic, age-related intraspecific communicative expression of threat or dominance, and is not typically observed in the precopulatory or copulatory sequences. It is a curious coincidence that human subjects treated for depression with the related tricyclic compound, clomipramine, experienced spontaneous orgasm in association with yawning [9]. Male subjects ejaculated during such episodes.

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