



Case Report

Effect of Pergolide Therapy on Semen Parameters in a Stallion With Pituitary Pars Intermedia Dysfunction

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ABSTRACT

A 23-year-old Warmblood stallion with pituitary pars intermedia dysfunction (PPID) was treated with 0.002 mg/kg body weight pergolide orally once a day, starting in July. Semen collections during 5 consecutive days each were performed before starting and at 90 days after initiation of the therapy in order to assess the effect of the therapy on semen volume, concentration, total sperm count, motility, and viability. The only changes observed were lowered semen volume compensated by increased semen density resulting in an equal total sperm count. Possible causes for these observations include altered prolactin levels, the influence of season, or pergolide acting directly on the ejaculation process. This case report provides first evidence that pergolide therapy in PPID may alter semen parameters, but these changes are unlikely to affect fertility. However, this observation in a single individual must be confirmed with experiments on multiple stallions.

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1. Introduction

Pituitary pars intermedia dysfunction (PPID) or equine Cushing syndrome is an endocrine disorder which mostly occurs in aged horses without a breed predisposition [1,2]. Hypertrichosis is the pathognomonic sign of PPID (55%–80% of cases) [1], but other clinical signs associated with PPID include polyuria and polydipsia, chronic infections, laminitis, catabolism of muscles that is in the back and abdominal region [2], as well as disturbances of the

reproductive functions with impaired fertility [1,3]. These reproductive problems have been observed in mares, namely inhibition of normal ovarian activity, small sized follicles, absence of a corpus luteum, flaccid uterus as well as problems to maintain a normal pregnancy [4]. Case reports suggest that pergolide treatment of PPID can restore reproductive function in those animals [4,5]. In contrast to these observations in mares, the effects of pergolide treatment on the male reproductive system have so far not been documented. In a recently published case report, no abnormalities were found in routine semen examinations of a 21-year-old PPID-affected stallion and no histopathological alterations were seen in the testicles. However, treatment effects of pergolide could not be investigated due to anticipated death of the stallion [6].

The pathogenesis of PPID is not fully understood. It is hypothesized that PPID mainly results from oxidative stress and neurodegeneration in the dopaminergic neurons of the hypothalamus causing a decrease in dopamine production. The loss of the negative control by dopamine in the pituitary pars intermedia leads to an excessive production of proopiomelanocortin-derived peptides [5,7]. It is still

Animal welfare/ethical statement: Clinical case at the Swiss Institute of Equine Medicine. The semen collection procedures were previously approved by the admission board of the EU-licensed AI-centre of the Swiss National Stud (CH-VD-AI-01E).

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unknown which specific endocrine changes lead to which clinical signs observed in horses affected with PPID, and more specifically, to which potential disturbances of the reproductive system. Prolactin seems to play a major role in humans suffering from diseases associated with the pituitary gland, but whether similar effects are also present in horses with PPID is unknown [8,9].

In PPID, pergolide, a long-acting dopamine agonist, is the medical therapy of choice [3]. Positive response to medication is evidenced by improvement of clinical signs and a decrease of plasma adrenocorticotrophic hormone (ACTH) concentration [3]. There is, to the authors' knowledge, no information regarding the effect of pergolide on the equine male reproductive system. This report describes the case of a stallion with PPID and compares the sperm quality and quantity before and after initiation of a therapy with pergolide.

2. Material and Methods

2.1. Animal, Anamnesis, Clinical/Endocrinological Findings, and Treatment

A 23-year-old Holstein stallion weighing 571 kg was presented with signs of hypertrichosis and a history of delayed shedding of the winter coat. Furthermore, he showed slight axial musculature atrophy and a cresty neck. Plasma ACTH measurement was performed in February because of suspected PPID. A venous ethylenediamine tetraacetic acid blood sample was collected and immediately centrifuged (3,000g; 10 minutes) in a special ethylenediamine tetraacetic acid plasma stabilization tube (ACTHstab-Mikrogefäß, ALOMED, Radolfzell-Böhringen, Germany). The plasma was then collected and sent to the laboratory (ALOMED, Radolfzell-Böhringen, Germany), where plasma ACTH concentration was measured using chemiluminescence immunoassay.

The ACTH plasma concentration was 87 pg/mL, suggesting a high probability for PPID in this horse [7,10]. The stallion was treated with 0.002 mg/kg body weight pergolide (Prascend, Boehringer Ingelheim, Basel, Switzerland) orally once a day starting the 18th July until his death 3 years later. A second blood analysis 6 months after initiation of pergolide therapy using the same approach revealed a plasma ACTH concentration (37 pg/mL) within the normal range based on the laboratory references [10], but still slightly above the upper threshold described in the study of McGowan et al [7] in 2013 (29.7 pg/mL).

2.2. Semen Evaluation

Two semen evaluation series took place from 9th to 13th July before and from 15th to 19th October 90 days after initiation of the pergolide treatment in order to compare the effects of the medication on semen parameters. Before each semen evaluation series, semen collections were performed one time per day for 5 consecutive days in order to deplete and stabilize the extragonadal sperm reserves as described by Thompson et al [11]. After a break of 1 day, semen was again collected daily once during 5 consecutive days, followed by a comprehensive semen evaluation of each ejaculate.

Ejaculates were collected using a dummy and an artificial vagina (type Avenches, Swiss National Stud, Avenches, Switzerland). Immediately after collection and removal of the gel fraction, the volume of the ejaculate was determined using a graduated container, the sperm concentration and viability (integrity of the sperm plasma membrane) were evaluated using a nucleocounter (NucleoCounter SP-100 Sperm Cell Counter, ChemoMetec A/S, Allerød, Denmark [12]), and total sperm number was calculated. Total and progressive motility were assessed in 10- μ L raw semen diluted with 20 μ L INRA 96 (IMV Technologies, L'Aigle, France) with a computer-assisted sperm analyzer (HTM-IVOS, version 12, Hamilton Thorn, Beverly, MA) using a 20- μ m standard count analysis chamber (Art. Nr. SC 20-01 C, Leja, Nieuw-Vennep, the Netherlands) and standardized threshold values for stallion semen.

2.3. Statistics

Statistical analysis was carried out using NCSS software (NCSS 2007, Statistical Solutions, Saugus). Semen volume, concentration, total sperm count, motility, and viability were normally distributed, and parametric paired *t*-tests were performed in order to assess the effects of treatment. Results were expressed as means \pm standard deviation of the average recordings before and after treatment. Values were considered to be statistically significant at a probability level of $P < .05$.

3. Results

After 90 days of therapy, improved hair coat quality and body condition were observed. No adverse side effects were witnessed during the course of the treatment. The stallion did not exhibit any behavioral changes during semen collection. Results of the spermatological analysis are illustrated in Table 1. The volume of the ejaculates was significantly higher in the samples collected before pergolide treatment compared to the samples collected after initiation of the therapy ($P = .003$). Semen concentration showed a tendency to be increased during the therapy ($P = .06$), while the other parameters showed no changes.

Table 1

Summary of the means \pm standard deviations (SDs) of various semen parameters collected over a period of 5 days each prior and after 90 days of oral pergolide treatment in a stallion.

Parameter	Before Pergolide Treatment		During Pergolide Treatment	
	Mean	\pm SD	Mean	\pm SD
Volume (mL)	62.2	9.4 ^a	33.4	12.1 ^b
Concentration ($\times 10^6$ sp/mL)	139.6	36.9	236.0	90.20
Total sperm count ($\times 10^9$ sp)	8.766	2.895	7.484	2.336
Total motility (%)	83.8	6.4	87.6	2.6
Progressive motility (%)	58.2	5.8	61.4	4.4
Viability (%)	88.0	2.0	87.8	0.8

Means with different superscripts (a, b) are significantly different ($P < .05$).

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