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Original Research

Effect of Repeated Cabergoline Treatment on the Vernal Transition and Hair Shedding of Mares (Year 1) and a Subsequent Comparison of the Effect of Starting Date on Prolactin Suppression (Year 2)

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ABSTRACT

Two studies were conducted to determine efficacy of cabergoline for suppressing prolactin (PRL) and the possible effects on vernal transition in mares. In experiment 1, six mares each received either vehicle or cabergoline (5 mg, intramuscularly) every 10 days for 12 treatments beginning February 4, 2013. Blood samples were drawn regularly, and mares were challenged with sulpiride periodically to assess PRL suppression. Weekly hair samples were obtained to determine shedding. Prolactin was suppressed ($P < .05$) by cabergoline, but suppression waned in spring. There was no effect ($P > .05$) of treatment on day of first ovulation, luteinizing hormone, or follicle stimulating hormone. Hair shedding was generally suppressed ($P = .05$). In 2014 (experiment 2), eight of the same 12 mares were used in a similar experiment to determine if the rise in PRL observed in experiment 1 was due to refractoriness to cabergoline or perhaps another factor. Treatment began on April 6, 2014, corresponding to the increase in PRL in treated mares in experiment 1. Mares were treated with cabergoline or vehicle until June 5. Prolactin was suppressed ($P < .05$) by cabergoline, and the pattern of apparent escape from suppression was similar to year 1. We conclude that (1) cabergoline at this dose alters hair shedding but does not alter the time of first ovulation in mares and (2) relative to our previous reports of cabergoline treatment in the fall, there is a seasonal effect on the ability of this dose of cabergoline to suppress unstimulated PRL secretion.

1. Introduction

Prolactin (PRL) appears to be involved in the vernal transition of seasonally anestrous mares, given that administration of exogenous PRL [1,2] or a dopamine antagonist [3–5] can initiate early follicular growth and hasten the date to first ovulation. Besognet et al [3] treated mares with the dopamine antagonist, sulpiride, and were able to increase PRL concentrations and advance the first ovulation of the season by approximately 20 days when compared to untreated mares. Subsequent researchers have tested both sulpiride and domperidone with varying degrees of success, advancing the first ovulation of the season by as much as 40 days [5]. In addition to the effects on reproduction, elevated PRL appears to also have a stimulatory effect on hair coat shedding [3,6].

The mechanisms involved with the ovarian response to PRL in seasonally anovulatory mares have not been elucidated. Localization of receptors for PRL on equine granulosa and theca cells [7] as well as the presence of PRL in follicular and luteal tissue [8,9] is supportive of a model in which PRL acts directly on the equine ovary during the vernal

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transition. Although much research has been devoted to administering dopamine antagonists, few experiments have described the effects of PRL suppression on the vernal transition in mares. Bennett-Wimbush [10] treated three groups of anestrous pony mares with perphenazine twice daily, bromocriptine daily, or vehicle from January 20 until ovulation. Perphenazine, a dopamine antagonist, advanced the first ovulation by 30 days compared to controls, whereas the dopamine agonist, bromocriptine, had no effect on time to first ovulation but did appear to delay growth of preovulatory sized follicles. Similarly, Bass [11] administered a long acting dopamine agonist, cabergoline, orally during the natural breeding season, which suppressed PRL concentrations but had little to no effect on ovulation or luteal progesterone production. Although both studies suppressed circulating PRL concentrations, neither daily bromocriptine nor oral cabergoline was able to completely suppress PRL for any length of time.

Recently, Hebert et al [12] reported complete suppression of PRL using cabergoline in a slow releasing vehicle injected intramuscularly. Even when challenged with a low dose of sulpiride 10 days after cabergoline injection, PRL remained suppressed. Additionally, Arana Valencia et al [13] administered a total of seven cabergoline injections 10 days apart and demonstrated no incidences of refractoriness to cabergoline in horses challenged with sulpiride (1 day before the next cabergoline injection) or side effects to the cabergoline compound. Based on those results, we hypothesized (experiment 1) that cabergoline in the same vehicle used in the experiments conducted by Hebert et al [12] and Arana Valencia et al [13] would suppress PRL in the long term and thus allow a better assessment of the need of circulating PRL in follicular growth and eventual ovulation in mares transitioning from winter anovulation to a breeding season state in the spring. Given the less-than-total suppression of PRL by cabergoline in late spring in experiment 1, experiment 2 was performed to test whether the lack of suppression was due to (1) a refractoriness of the mares to long-term cabergoline exposure or perhaps (2) some seasonal change in the mares made them less susceptible to cabergoline suppression.

2. Materials and Methods

Procedures used in these experiments were approved by the Institutional Animal Care and Use Committee of the Louisiana State University Agricultural Center.

2.1. Animals and Treatments

All mares in the two experiments were routinely maintained outdoors on native grass pasture during the warmer months and were grazed on winter ryegrass pasture when available in late winter. In the period between availability of summer grasses and winter ryegrass, hay prepared from the same native grasses was provided for ad libitum consumption as needed.

Before the start of the first experiment, all nonpregnant mares in the resident herd were assessed by ultrasonic scanning of the ovaries once a week for 3 weeks starting January 20, 2013, and samples of jugular blood were collected every 4 days. Anovulation was defined as the absence of any follicle >20 mm, the absence of any corpora lutea, and plasma progesterone concentrations consistently less than 1 ng/mL.

2.1.1. Experiment 1

Twelve light horse, anovulatory mares were identified and were allotted into two similar groups based on age (4–23 year old), body condition score (4–7), and ovarian follicular growth before start of the experiment (February 4, 2013). The groups were then randomly assigned as treatment (n = 6) and control (n = 6).

On February 4, 2013, and every 10 days thereafter for a total of 12 injections, mares assigned to the treatment group received 5 mg of cabergoline (Attix Pharmaceuticals, Toronto, Ontario, Canada) intramuscularly in a slow-release vehicle (1 mL). Mares assigned to the control group received vehicle only (1 mL), intramuscularly, on the same schedule. The vehicle was a proprietary mixture of hydrophobic, oily liquids designed to provide sustained, slow release of cabergoline over time (Provided by Richard M. Gilley, BioRelease Technologies LLC, Birmingham, AL).

2.1.2. Experiment 2

Eight of the same 12 mares from experiment 1 were available and were used the following year. Mares remained in the same treatment groups in both experiments. On April 6, 2014, and every 10 days thereafter, mares in the treatment group (n = 4) received cabergoline as described in experiment 1. Mares assigned to the control group (n = 4) received vehicle only. A total of seven treatment injections were given, with the last injection on June 5, 2014.

2.2. Ultrasonography and Estrous Behavior

In experiment 1, ovarian activity was monitored via ultrasonography (Aloka 550V with 5-Mhz linear-array transducer; Hitachi-Aloka, Wallingford, CT) once a week until a follicle >25 mm emerged. Once a follicle exceeded 25 mm, the mare was scanned daily until the follicle ovulated or regressed to <25 mm.

Also on detection of a follicle >25 mm, the mare was checked for displays of estrus with one of two stallions daily until 2 days after her second ovulation. A single evaluator graded receptivity of the mare using a −3 to 3 scale, whereby, −3 = extreme aggression toward stallion, −2 = ear pinning, −1 = avoidance of stallion, 0 = indifferent to stallion, 1 = raising tail, 2 = raising tail as well as clitoral eversion, and 3 = posturing and urinating.

In experiment 2, only the PRL response to cabergoline was characterized. Given the lack of effect on reproduction in experiment 1, ultrasonography, estrus detection, and circulating gonadotropins were not assessed in experiment 2.

2.3. Blood Sampling

2.3.1. Experiment 1

Jugular blood samples were collected in 10-mL evacuated tubes containing sodium heparin (Vacutainer, Becton and Dickinson, Franklin Lakes, NJ) beginning on Feb 5, 2013