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Original Research

Inhibitory Effects of Pergolide and Cabergoline Formulations on Daily Plasma Prolactin Concentrations in Geldings and on the Daily Prolactin Responses to a Small Dose of Sulpiride in Mares

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ABSTRACT

Two experiments were conducted to assess the efficacy and duration of action of two dopaminergic compounds, pergolide and cabergoline, on daily prolactin secretion in geldings and on prolactin responses to a small dose of sulpiride over 10 days. In the first experiment, oral administration of 2 mg of pergolide was compared to a single injection of 2 mg of pergolide in a slow-release vehicle and a single injection of 5 mg of cabergoline in slow-release vehicle. Controls received vehicle only. All drug treatments reduced ($P < .05$) prolactin concentrations relative to that in controls but differed substantially in duration of action (oral pergolide approximately 6 hours or less, injected pergolide 6 to 24 hours, and injected cabergoline at least 6 days). In the second experiment, repeated small doses of sulpiride (2 μg/kg of body weight intravenously) were used to stimulate prolactin release in mares, and the ability of seven daily injections of pergolide (2 mg each) and a single injection of cabergoline (5 mg) in slow-release vehicle to suppress this release were compared. Control mares receiving vehicle injections had robust prolactin responses to the sulpiride injections on all days of injection (days 1, 0, 1, 2, 3, 4, 6, 8, and 10 relative to treatment). Prolactin responses were muted ($P < .05$) by pergolide and cabergoline treatments on the first day of injection (day 0, 30 min after treatment) and were basically absent on days 1 to 8. The single injection of cabergoline continued to be suppressive through day 10, whereas mares previously treated with pergolide (through day 6) had begun to recover a prolactin response by day 10. We conclude that either daily 2-mg pergolide injections in slow-release vehicle or a single injection of 5 mg of cabergoline in slow-release vehicle is an effective way to apply dopaminergic activity to horses for approximately 7 to 10 days and may have application in the treatment of pituitary pars intermedia dysfunction in affected horses.

1. Introduction

Pergolide is a dopamine receptor agonist that was removed from the US market for human use due to its association with heart valve dysfunction [1]. However, it has recently been approved for use in horses as a treatment for pituitary pars intermedia dysfunction (PPID) in horses [2].

Cabergoline is another dopamine receptor agonist that is highly active on dopaminergic type D2 receptors [3]. It was also commercially available for human use and went off patent in 2005 but has the same potential side effects as pergolide [1]. It may be a potential replacement for pergolide for use in horses due to its long-acting nature [4].

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In the first phase of the current research [5], we demonstrated that either estrogen-primed geldings in spring or cyclic mares in summer provided a possible paradigm for the assessment of the efficacy and duration of activity of dopamine agonists for suppression of the prolactin responses to repetitive small doses of sulpiride. Prolactin secretion from the lactotropes of the anterior lobe of the adenohypophysis is controlled by tonic suppression by hypothalamic dopamine input in the same manner as α-melanocyte stimulating hormone (MSH) secretion from the melanotropes of the intermediate lobe [6,7,8]. Thus, we proposed that measuring drug effects on prolactin secretion could serve as an alternative to monitoring MSH concentrations, thereby providing researchers flexibility in their experimental approach.

Two experiments were conducted herein. The first experiment was designed to determine and compare the effects of the current drug of choice, pergolide, in two possible formulations (oral administration and intramuscular injection) to those of cabergoline (injected) on unstimulated daily plasma prolactin concentrations in geldings. Based on those results, the second experiment compared the efficacy of daily pergolide injections to a single injection of cabergoline for suppression of prolactin responses to small doses of sulpiride in mares.

2. Materials and Methods

All procedures described herein were approved by the Institutional Animal Care and Use Committee of the LSU Agricultural Center. The mares and geldings used were of light horse breeds and were long-term residents of the LSU Agricultural Center horse farm in Baton Rouge, LA. They were routinely kept on native grass pasture most of the year and on winter ryegrass pasture when native grasses were dormant; grass hay was provided in transitional periods when grasses were insufficient to maintain body conditions. The horses remained on pasture except when experimental procedures were being performed.

2.1. Experiment 1

Sixteen light horse, long-term geldings were used. They ranged in age from 6 to 20 years old, weighed between 410 and 616 kg, and had body condition scores [9] between 5 and 8.

The 16 geldings were randomly assigned to one of four treatment groups (n = 4/group): control (received 2 mL of vehicle), pergolide injection (received 2 mg in 2 mL of vehicle), cabergoline injection (received 5 mg in 1 mL of vehicle), and oral pergolide administration (received one 2-mg capsule). Pergolide capsules were obtained from BET Pharm (BETpharm.com) and used as supplied. Pergolide mesylate (USP; Letco Medical, Decatur, AL; letcomedical.com) and cabergoline (Attix Pharmaceuticals, Toronto, Ontario, Canada) were each formulated in a proprietary mixture of hydrophobic, oily liquids designed to slow down and produce a sustained release of drug over time, similar (but not identical) to the vehicle used for LA 300 progesterone (BioRelease; BETpharm.com) [10]. Control injections were vehicle only.

All geldings were treated at 8:00 AM on August 20, 2011. All injections (treatments and vehicle) were given intramuscularly and pills (oral pergolide) were administered with the aid of a pill gun; geldings not receiving oral treatment had the pill gun placed into their mouth to equalize stress levels across treatments, and geldings given oral pergolide received an injection of vehicle. The geldings were kept in a small pasture close to the site of treatment so they were easily accessible for blood collection (to avoid stress or running before blood collection). On the morning of treatment and for every blood collection that day, they were loosely tethered in an outdoor chute.

Blood samples were obtained via jugular venipuncture into heparinized, evacuated tubes 12 and 24 hours before treatment and then immediately before injection (time 0 on day 0); then at 1, 3, 6, 9, and 12 hours after injection; and every 12 hours thereafter until the morning of day 6. Plasma was harvested from all samples by centrifugation (1200 × *g* for 15 min) and was stored at −15°C. Prolactin was measured in all plasma samples as described by Colborn et al [11]. Briefly, the assay was based on a rabbit anti-porcine prolactin antiserum and a highly purified equine prolactin preparation used for radioiodination and the reference standard. Intra- and interassay coefficients of variation and limit of detection were 7%, 12%, and 0.1 ng/mL, respectively.

Prolactin concentrations were analyzed using one-way analysis of variance (ANOVA) with repeated measures (sampling times) with treatment and time as main effects (SAS software; SAS Institute, Cary, NC). Treatment effect was tested with the animal-within-treatment term, and time and interaction were tested with residual error. The significance of differences between groups for each time period was tested by the least significant difference test [12].

2.2. Experiment 2

Fifteen light horse mares were used for experiment 2. They ranged in age from 5-16 years old, weighed between 480 and 616 kg, and had body condition scores between 5 and 8. Mares were initially assigned to one of three groups of five based on their ages, body weights, and body condition scores, such that the means for those characteristics in the three groups were similar. The groups were then randomly assigned to (1) controls (vehicle injected); (2) daily pergolide injections (2-mg injections daily for 7 days); and (3) a single injection of cabergoline (5 mg in vehicle). Control mares received single intramuscular injections of vehicle daily from day 0 through day 6. Cabergoline-injected mares received the single intramuscular injection of cabergoline in slow-release vehicle on day 0 and then injections of vehicle from days 1 through day 6. Pergolide-injected mares received single daily intramuscular injections of pergolide in slow-release vehicle on days 0 through 6. All injections were given in the morning between 7:00 and 8:00 AM.

The small-dose sulpiride challenges (2 μg/kg of body weight of the [dl]-racemic mixture in saline administered intravenously) were started on day −2 (October 19, 2011) and were repeated on days −1, 0, 1, 2, 3, 4, 6, 8, and 10. The original experimental protocol called for daily sulpiride challenges through day 10 but several mares became averse