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Using domperidone to induce and sustain hyperprolactinemia in late-pregnant gilts

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ABSTRACT

Prolactin controls mammary development as well as the lactogenic and galactopoietic processes in sows and increasing prolactin during gestation can augment milk yield. The dopamine receptor antagonist domperidone can increase circulating prolactin concentrations in pigs, but the ideal dose to achieve sustained hyperprolactinemia remains unknown. An experiment was performed to develop a protocol for using domperidone in studies of rapid and sustained hyperprolactinemia in late-pregnant gilts. On day 90 of gestation, gilts were divided into 4 groups: (1) intramuscular (IM) injections of canola oil (3 mL, controls [CTL], n = 9), (2) IM injections with 0.1 mg/kg BW of domperidone (LO, n = 8), (3) IM injections with 0.5 mg/kg BW of domperidone (ME, n = 11), and (4) IM injections with 1.0 mg/kg BW of domperidone (HI, n = 11). Injections were given daily at 8:05 from days 90 to 109 of gestation. Treated gilts also received domperidone per os (0.5 mg/kg BW) at 8:00 and 20:00 on days 89, 90, and 91 of gestation. Three jugular blood samples were collected from all gilts at 6-h intervals on days 89, 90, and 91 of gestation, then twice daily on days 92, 93, and 94. Thereafter, samples were obtained at 8:00 every other day until day 114 of gestation. Blood was sampled serially from 9 CTL and 11 HI gilts on days 89 and 94 of gestation. On day 89 of gestation, prolactin concentrations for LO, ME, and HI gilts increased within 6 h of domperidone per os ($P < 0.001$). From days 89 until 93 of gestation, the area under the curve (AUC) for LO, ME, and HI gilts was greater than that for CTL gilts ($P < 0.001$), whereas from days 89 until 114, ME and HI gilts had greater AUC than CTL and LO gilts ($P < 0.05$). Results demonstrate that the combination of per os treatment with IM injections of 0.5 mg/kg of domperidone in an oil emulsion leads to the rapid and sustained release of prolactin over 24 d in late-pregnant gilts. Higher doses of domperidone failed to further increase circulating prolactin levels. These findings provide a useful strategy to induce sustained hyperprolactinemia in late-pregnant gilts.

1. Introduction

Prolactin has a range of biological functions including its role in lactation as well as in metabolism, osmoregulation, behavior, and immunoregulation [1]. Prolactin is mainly secreted by lactotrophs of the anterior pituitary and has a unique neuroendocrine control where it is predominantly under hypothalamic inhibition due to the effects of dopamine [2]. Indeed, dopamine agonists are given to inhibit prolactin secretion [3–5], whereas dopamine antagonists increase circulating prolactin [6,7].

In swine, prolactin affects sow milk yield by playing an essential role in mammary development during late gestation [3,4] and in the initiation as well as the maintenance of milk production [5]. Recent results also suggest a relationship between circulating prolactin concentrations

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30 to 40 h prepartum and colostrum yield in sows [8]. Furthermore, VanKlompenberg et al [7] reported a 21% greater growth rate in suckling piglets born from gilts that received twice daily treatment with 0.4 mg/kg of domperidone per os from days 90 to 110 of gestation. However, that treatment only realized a transient increase in prolactin from days 91 to 96 of gestation and did not lead to sustained hyperprolactinemia. On the other hand, greater prolactin levels that were sustained over a 5-wk treatment period were achieved in dairy cattle following injections with domperidone suspended in canola oil [9], yet the initial increase was slower than when domperidone was fed to gilts [7]. Both dose and frequency of treatment as well as route of administration (per os vs intramuscular [IM] injection) can influence the synthesis and secretion of prolactin in response to domperidone treatment [10]. The objective of the present study was to establish dose-response kinetics in gestating gilts following combined early per os treatment with repeated IM injections of domperidone in an oil emulsion to assess the sustenance of hyperprolactinemia.

2. Materials and methods

Animals were cared for according to a recommended code of practice [11], and procedures were approved by the institutional animal care committee.

2.1. Animals and treatments

Thirty-nine Yorkshire × Landrace gilts were bred via artificial insemination with semen from a pool of Duroc boars. On day 88 of gestation, a catheter was inserted nonsurgically in the jugular vein of all gilts, as described by Matte [12]. Gilts were then divided into 4 groups to receive (1) IM injections of canola oil (3 mL, controls [CTL], n = 9), (2) IM injections of domperidone at 0.1 mg/kg BW (LO, n = 8), (3) IM injections of 0.5 mg/kg BW of domperidone (ME, n = 11), and (4) IM injections of 1.0 mg/kg BW of domperidone (HI, n = 11). Injections were given daily at 8:05 from days 90 to 109 of gestation.

The domperidone (Glentham Life Sciences, Corsham, Wiltshire, UK) was resuspended in canola oil and injected as an emulsion (3 mL) that was prepared twice weekly. Doses were based on the average BW of gilts (208.2 ± 9.1 kg, mean ± SD) on day 88 of gestation. Treated gilts also received 0.5 mg/kg BW of domperidone (JAMP Pharma Corp., Boucherville, QC, Canada) per os (in a ball of corn) twice daily (8:00 and 20:00) on days 89, 90, and 91 of gestation. The per os route was chosen to realize a rapid increase in serum prolactin concentrations, whereas the IM injection in canola oil was chosen to achieve a sustained release of prolactin over several weeks. Gestating gilts were housed in individual stalls (0.6 m × 2.1 m) and were fed a commercial corn-soy diet containing 12.5% CP, 12.8 MJ/kg DE, and 0.3% lysine. Amount fed was adjusted according to their body condition at mating. Gilts received one daily meal of 2.25 or 2.05 kg for back fat thicknesses of 15 to 17 mm, and >18 mm, respectively. From day 100 of gestation, all animals received an extra 1 kg of feed per day. Gilts were weighed and had their back fat thickness measured ultrasonically at P2 of the last rib (WED-3000, Shenzhen WELL D Medical Electronics Co., Ltd., Shenzhen, China) on days 88 and 110 of gestation. Gilts were transferred to farrowing crates on day 110 of gestation and litters standardized to 11 ± 1 piglets within 48 h of farrowing. Lactating sows were fed a 19.7% CP commercial corn-soy diet (14.8 MJ/kg DE and 1.0% lysine) in 2 meals at 8:00 and 15:00 daily. Gilts received 1.6 kg of this diet on the day of farrowing and were fed this same diet ad libitum through the remainder of lactation. Refusals were weighed daily to determine feed intakes.

2.2. Blood and milk samplings

Blood was sampled from the jugular vein of all gilts thrice daily on days 89, 90, and 91 of gestation. Sampling occurred before the morning per os administration of domperidone, then 6 and 12 h later (before the evening per os delivery). Two blood samples were also obtained from the jugular vein twice daily on days 92, 93, and 94 of gestation in the morning (before the IM injection) and then 6 h later. Thereafter, blood samples were collected in the morning before the IM injection every other day until day 114 of gestation.

Blood was sampled serially from the jugular vein of 9 CTL and 11 HI gilts on days 89 and 94 of gestation. The first blood sample was obtained just before the morning delivery of domperidone (T0; domperidone given per os on day 89 or IM on day 94), followed by sampling 15, 30, 45, and 60 min later, then at hourly intervals across a 12-h period. Concentrations of prolactin were measured in all blood samples.

Representative milk samples were obtained from all sows on day 3 of lactation by hand milking. Milk collected from 3 functional glands (anterior, middle, and posterior) that were emptied following an intravenous (IV) injection of 1.0 mL of oxytocin (20 IU/mL; P.V.U. Victoriaville, QC, Canada) were pooled before sampling. Piglets were separated from their dam for 40 min before oxytocin was injected.

2.3. Blood handling, prolactin assay, and milk compositional analyses

Blood samples (5 mL) were collected into Vacutainer tubes without anticoagulant (Becton Dickinson, Franklin Lakes, NJ) and left at room temperature for 3 h, stored overnight at 4°C, centrifuged for 12 min at 1,800 × *g* at 4°C the following day, and serum was harvested and frozen at −20°C until assayed. Concentrations of prolactin were determined according to a previously described RIA [13]. The radioinert prolactin and the primary antibody to prolactin (raised in rabbit) were purchased from A. F. Parlow (U.S. National Hormone and Pituitary Program, National Institute of Diabetes and Digestive and Kidney Diseases, Torrance, CA). Assay validation was performed using pooled serum from gestating gilts. Parallelism was 99.2% and average mass recovery was 99.5%. Sensitivity of the assay was 1.5 ng/mL. The intra- and interassay CV were 4.45% and 7.79%, respectively.