J. Dairy Sci. 99:1–12
http://dx.doi.org/10.3168/jds.2015-10782

Cabergoline inhibits prolactin secretion and accelerates involution in dairy cows after dry-off

M. Boutinaud,*†[1] N. Isaka,‡ V. Lollivier,*†§ F. Dessauge,*† E. Gandemer,*† P. Lamberton,*† A. I. De Prado Taranilla,‡ A. Deflandre,‡ and L. M. Sordillo#
*INRA, UMR1348 Pegase, F-35590 Saint-Gilles, France
†Agrocampus-Ouest, UMR1348 Pegase, F-35000 Rennes, France
‡Ceva Santé Animale, F-33500 Libourne, France
§Université Européenne de Bretagne, F-35000 Rennes, France
#Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, East Lansing 48824

ABSTRACT

Dairy cattle require a dry period between successive lactations to ensure optimal milk production. Because prolactin (PRL) is necessary for the initiation and maintenance of milk production, strategies that can inhibit PRL secretion might hasten the involution process. The objective of this study was to determine the effect of the PRL release inhibitor cabergoline on markers of mammary gland involution during the early dry period. To assess the effect of cabergoline treatment on mammary gland involution, 14 Holstein dairy cows in late lactation were treated with either a single i.m. administration of 5.6 mg of cabergoline (Velactis, Ceva Santé Animale, Libourne, France, n = 7) or placebo (n = 7) at the time of dry-off. Blood samples and mammary secretion samples were collected 6 d before dry-off and again 1, 2, 3, 4, 8, and 14 d following the abrupt cessation of lactation. Blood samples were used to determine plasma PRL concentrations. Mammary secretion samples were used to determine somatic cell count, milk fat, lactose, true protein content, and concentrations of α-lactalbumin, lactoferrin, and citrate. Following the cessation of lactation, changes in mammary secretion composition indicated diminished milk synthesis, including reduced concentrations of α-lactalbumin, citrate, and lactose. In contrast, milk somatic cell count, percent total protein, percent fat content, and lactoferrin concentrations significantly increased as involution progressed. Cabergoline treatment decreased the plasma PRL concentrations during the first week of dry-off, compared with the control treatment. No significant differences in citrate, α-lactalbumin, or protein content were observed between treatment groups. The most dramatic changes in secretion composition as a consequence of cabergoline treatment occurred during the first week of the dry period, when lactose concentrations and the citrate:lactoferrin molar ratio were lower and lactoferrin concentrations higher than in the control cows. Cabergoline treatment also tended to increase fat content and somatic cell count more rapidly following dry-off compared with the control group. These changes in mammary secretion composition following the abrupt cessation of lactation indicate that cabergoline treatment facilitated dry-off and effectively accelerated mammary gland involution.
Key words: mammary gland, dairy cow, drying-off, prolactin, involution

INTRODUCTION

The dry period is an important phase of a dairy cow's lactation cycle and is routinely implemented on most dairy farms. Previous studies clearly document the importance of a dry period lasting 40 to 60 d for optimal milk production (Collier et al., 2012). The overall benefits derived from the dry period are thought to be a consequence of adequate mammary gland secretory cell turnover and differentiation between consecutive lactations (Capuco et al., 2003). Although the dry period is essential from the standpoint of lactation physiology, the abrupt cessation of lactation has become problematic with the modern dairy cow, which may produce 25 to 30 kg/d of milk at the time of dry-off (Stefanon et al., 2002). Researchers have shown that high-producing dairy cows are more susceptible to new intramammary infection during the early dry period (Rajala-Schultz et al., 2005). This susceptibility can be related to excessive accumulation of milk at the time of dry-off, which may lead to milk leakages (Zobel et al., 2015) and reduce the functional capabilities of mammary leukocyte populations (Oliver and Sordillo, 1989). Fully involuted mammary glands are more resistant to new bacterial infections, and the mammary glands of cows entering

Received December 18, 2015.
Accepted March 30, 2016.
[1]Corresponding author: marion.boutinaud@rennes.inra.fr

the dry period with lower milk production involute at a faster rate than those of high-producing dairy cows (Bushe and Oliver 1987; Oliver and Sordillo, 1989). Moreover, excessive mammary gland engorgement at the time of dry-off in high-producing dairy cows may be a significant source of discomfort and pain (O'Driscoll et al., 2011; Silanikove, 2014). The dairy industry needs practical management strategies to effectively dry off high-producing dairy cows at the end of their lactations.

Upon abrupt cessation of lactation, the bovine mammary gland undergoes complex molecular and cellular changes that are needed to ensure optimal milk production in the subsequent lactation (Capuco and Akers, 1999; Kuhn et al., 2006; Watters et al., 2008). Cessation of milk removal initiates the involution process, which includes udder engorgement and increased intramammary pressure (Hurley, 1989). Changes in mammary tissue morphology and function begin at dry-off; some changes are rapid, whereas others are progressive, such as a decrease in secretory cell activity, an increase in epithelial cell turnover, and the infiltration of leukocytes into mammary tissue spaces to remove cellular debris (Hurley, 1989; Oliver and Sordillo, 1989). Changes in the composition of mammary secretions during the onset of involution reflect a rapid decline in mammary epithelial cell function; these changes include a reduction in major milk constituents, such as lactose and casein. In contrast, lacteal concentrations of factors associated with mammary gland defenses, such as leukocytes and the bacteriostatic whey protein lactoferrin, progressively increase (Hurley, 1989; Oliver and Sordillo, 1989; Kutila et al., 2003). The most rapid changes in bovine mammary tissue morphology and function occur within the first week of the dry period, whereas the complete transition from a lactating to nonlactating state is thought to be completed 3 to 4 wk following the abrupt cessation of lactation (Holst et al., 1987; Hurley, 1989).

Milk stasis and distension of mammary secretory tissues are thought to contribute to the involution process through local chemical feedback by milk constituents, formation of other inhibitor factors in secretions, and mechanical stress to alveolar cells that can lead to the loss of secretory function (Collier et al., 2012). However, the maintenance of lactation is also under endocrine control by galactopoietic hormones such as prolactin (**PRL**; Lacasse et al., 2016). Prolactin is mainly produced by the lactotrophs of the anterior pituitary under the negative control exerted by dopamine (Ingram et al., 1986). A surge of PRL is released into plasma not only at parturition, but also at each milking (Koprowski and Tucker, 1973). Recent evidence supports this galactopoietic role for PRL, as this hormone is essential for maintaining lactation and its suppression strongly inhibits lactation in ruminants (Lacasse et al., 2016). The ability of dopamine agonists to inhibit PRL secretion is a factor in suppressing unwanted lactation in women and female dogs (de Groot et al., 1998). In cows, the inhibition of PRL secretion by the pituitary gland after daily injections of quinagolide, a dopamine agonist, was also shown to reduce milk yield during established lactation (Lacasse et al., 2011; Lollivier et al., 2015). This decrease in milk yield was associated with lower levels of milk protein mRNA, in conjunction with reduced mammary epithelial cell survival and proliferation (Boutinaud et al., 2012). In contrast, PRL injections restored mammary epithelial cell proliferation and survival (Lollivier et al., 2015). In addition, injections of quinagolide at dry-off were shown to accelerate mammary gland involution (Ollier et al., 2013). Thus, inhibiting PRL secretion may be one approach to facilitating mammary gland involution in dairy cattle at dry-off.

Another powerful dopamine agonist, cabergoline, is an ergot derivative that has a high affinity for D2 dopamine receptors. Cabergoline is used in women to treat hyperprolactinemia (Crosignani, 2006) and suppress lactation (de Groot et al., 1998; Gobello, 2006). A recent study reported that a single injection of cabergoline is able to reduce plasma PRL concentrations in dairy cows at dry-off (Bach et al., 2015). In addition, the cabergoline treatment at dry-off also reduced udder engorgement (measured by a digital algometer), decreased the incidence of milk leakage, and improved lying time the day following dry-off (Bach et al., 2015). To date, however, how cabergoline acts on milk synthesis during the early stages of involution is unknown. Thus, the objective of this study was to determine whether treating cows with cabergoline at the time of dry-off could accelerate mammary gland involution during the early dry period.

MATERIALS AND METHODS

Animals and Experimental Design

All the procedures applied to animals were approved by the Animal Care Committee of the French Ministry of Agriculture and were in accordance with French regulations (Decree No. 2001–464, May 26, 2001). The study was designed and performed in compliance with European VICH Topic GL9 (GCP): Good Clinical Practice.

Fourteen multiparous Holstein cows (644 ± 16.8 kg of BW) with 323 ± 21.6 DIM producing 16.8 ± 0.91