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Magnitude and Duration of Effects of Two Corticosteroid Formulations (Dexamethasone Sodium Phosphate and Phenyl Propionate; Prednisolone Acetate) on Blood Glucose, Leukocyte Values, and Milk Yield in Dairy Cows

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Abstract

The magnitude and duration of the effects of two corticosteroid formulations were determined on blood glucose and leukocyte values and milk yield in normal, lactating dairy cows. One formulation contained a combination of dexamethasone sodium phosphate and dexamethasone phenyl propionate (DEX). The other contained prednisolone acetate (PRED). Blood samples were obtained prior to and at 6, 24, 48, 72, 96, and 144 hours following administration of a single dose of DEX or PRED. Milk yield was determined for two days prior to drug administration and for seven days afterwards.

Both corticosteroids caused significant increases in blood glucose values, although DEX caused significantly larger and longer lasting increases. DEX also caused significant leukocytosis and neutrophilia. PRED caused significant, very short lasting neutrophilia, but had no significant effect on total blood leukocyte values. Both drugs caused significant reductions in blood eosinophil and lymphocyte values, and significant increases in monocyte values. DEX also caused a significant, marked drop in milk production on days 1, 2, and 6, post-administration. PRED did not significantly affect milk production.

Because DEX produced more dramatic and persistent changes in blood glucose values and milk production than did PRED, the authors believe that DEX is likely to be more efficacious than PRED for treating ketosis in dairy cows. Because DEX produced more dramatic and persistent effects on blood neutrophil values than PRED, it is also likely to be a better option for use as an anti-inflammatory drug.

Key words: dairy cows, glucocorticoids, dexamethasone, prednisolone

Résumé

L'ampleur et la durée des effets de deux formulations de corticostéroïdes sur la concentration sanguine de glucose et de leucocytes et sur la production de lait ont été examinées chez des vaches laitières normales en lactation. Une des formulations contenait une combinaison de phosphate de sodium de dexaméthasone et de dexaméthasone phénylpropionique (DEX) alors que l'autre contenait de l'acétate de prednisolone (PRED). Des échantillons sanguins ont été obtenus avant et 6, 24, 48, 72, 96 et 144 heures suivant l'administration d'une dose unique de DEX ou de PRED. La production de lait a été déterminée sur une période de deux jours avant l'administration des drogues et sur une période de sept jours par la suite.

Les deux corticostéroïdes ont causé une augmentation de la concentration du glucose sanguin bien que le traitement DEX ait entraîné une augmentation plus forte et plus longue. Le traitement DEX a aussi causé une leucocytose et une neutrophilie significatives. Le traitement PRED a causé une neutrophilie significative mais de très courte durée et n'avait pas d'effet significatif sur le nombre total de leucocytes sanguins. Les deux drogues ont entraîné des réductions significatives du nombre d'éosinophiles et de lymphocytes sanguins et une augmentation significative du nombre de monocytes. Le traitement DEX a aussi causé une réduction significative marquée de la production laitière aux jours 1, 2 et 6 suivant l'administration. Le traitement PRED n'a pas affecté la production de lait.

En raison des changements plus dramatiques et persistants du traitement DEX par rapport au traitement PRED sur la concentration sanguine du glucose et sur la production de lait, les auteurs croient que le traitement DEX est probablement plus efficace que le traitement PRED pour le traitement de l'acétonémie chez les vaches laitières. En raison des changements plus dramatiques et persistants du traitement DEX par rapport au traitement PRED sur le nombre de neutrophiles sanguins, ce traitement est donc probablement aussi une meilleure option comme drogue anti-inflammatoire.

Introduction

Corticosteroids are among the most used and most misused drugs in veterinary medicine. Even so, scientifically verified information concerning corticosteroid therapy is scarce for most species of domestic animals, especially regarding optimal dosages, treatment intervals, efficacy, and side effects. Frequently, therapeutic recommendations for veterinary use of corticosteroids are based on uncontrolled clinical experiences of individual veterinary clinicians, or on information obtained from clinical trials in man or other species.[6] The well-documented euphoric effect of corticosteroids can be a valid reason for their use.[15]

The clinical problems for which bovine practitioners most often use corticosteroids include: 1) ketosis in dairy cows, 2) calving paralysis (i.e., paralysis involving the sciatic, obturator or peroneal nerves), 3) aseptic laminitis, 4) localized post-surgical or post-traumatic inflammatory reactions, and 5) severe inflammation associated with infectious processes. In these instances corticosteroids are used in combination with appropriate bactericidal antimicrobial drugs.[24]

The range of effects of corticosteroids reported[2,9,15,18] in various species of animals include:

- Effects on carbohydrate, protein, and lipid metabolism: 1) increased protein catabolism and gluconeogenesis, 2) decreased peripheral utilization of glucose (insulin antagonism), and 3) decreases in lipid reserves.
- Anti-inflammatory effects: 1) increases in number of circulating neutrophils, 2) decreases in number of circulating lymphocytes and eosinophils, and 3) reductions in localized inflammatory effects.
- Mineralocorticoid effects: 1) increased sodium, chloride, and water retention, and 2) increased potassium, phosphorus, and calcium excretion.
- Reproductive effects: 1) induction of normal parturition in late-term bovine pregnancies, and 2) induction of abortions in cattle, after the 180th day of gestation, when used in combination with a prostaglandin.
- Effects on the immune system: 1) immunosuppression, and 2) alleviation of the clinical manifestations of certain immune-mediated diseases.

In order to establish a rational therapeutic regimen for a particular corticosteroid, it is important to consider the duration and magnitude of the effects. A major objective of this study was to investigate the duration of the effects of two previously untested corticosteroids, DEX and PRED, on milk production and on several blood parameters, as an indication of their metabolic action (glucose) and anti-inflammatory activity (total leukocytes, neutrophils, eosinophils, monocytes, and lymphocytes).

This study is the first report in which a combination of short-lasting and long-lasting glucocorticoids was administered to dairy cattle. It is also the first report of administration of dexamethasone sodium phosphate and dexamethasone phenyl propionate (DEX) and prednisolone acetate (PRED) to cattle, and the effects on blood glucose and leukocyte values and milk yield.

Materials and Methods

Twelve normal Holstein cows were randomly selected from a herd of approximately 200 lactating dairy cattle. All were between two and eight years of age, weighed between 1,210 and 1,595 lb (550 and 725 kg; average weight 1,450 lb or 659 kg), were producing between 51 and 117 lb (23 and 53 kg) (average of 84 lb or 38 kg) of milk per day, and had calved at least 65 days previously.

A single intramuscular injection of DEX[a] was administered to four cows at a dose of 0.027 mg/lb (0.06 mg/kg). DEX was a suspension in which each mL of water contained 1 mg of dexamethasone sodium phosphate and 2 mg of dexamethasone phenyl propionate. Other chemicals included in each mL of DEX formulation were trisodium citrate (11.4 mg), benzilic alcohol (10.4 mg), sodium chloride (4 mg), tragacantha (1 mg), methylcellulose MH50 (0.4 mg), and dimethicone (0.08 mg). The label specified a dose of 10 mL for an adult dairy cow. We assumed that the average weight of such a cow would be 1100 lb (500 kg), and calculated that such a cow should receive 30 mg of combined drug, which is a dose of 0.027 mg/lb (0.06 mg/kg). The label indicated that DEX had both short (sodium phosphate) and long-acting (phenyl propionate) effects.

A single intramuscular injection of PRED[b] was administered to four different cows at a dose of 0.18 mg/lb (0.40 mg/kg). PRED was a suspension of prednisolone acetate crystals in which each mL of water contained 10 mg of prednisolone acetate. Other chemicals included in each mL of PRED formulation were benzilic alcohol (9.45 mg), sodium chloride (9 mg), polysorbate 80 (4

mg), carboxymethylcellulose (3 mg), and dimethylpolysiloxane antifoam (1 mg). The label specified a dose of 10 to 20 mL for an adult cow. We assumed that the weight of such a cow would be 1100 lb (500 kg), chose to use the 20 mL (200 mg) dose, and calculated that the cow would receive 200 mg, which is a dose of 0.18 mg/lb or 0.4 mg/kg. The label indicated that PRED has a short-acting effect.

Both drugs are registered in several European countries for use in horses, cattle, sheep, goats, pigs, dogs, and cats, and have label recommendations for use in allergic reactions, non-infectious inflammatory processes, osteoarthritis, shock, ketosis, and pregnancy toxemia. Recommended milk and meat withdrawal periods for DEX and PRED were zero and eight days, and one and eight days, respectively.

A single intramuscular injection of physiological saline solution (20 mL) was administered to the remaining four cows. Cows were randomly allocated to the three treatment groups.

The study (excepting blood leukocyte counts) was performed on the farm, and subject cows were allowed to roam freely with their herd mates during the study. All cattle on this farm were tested annually for bovine leukemia virus (BLV), and the herd was considered to be free of this disease. Cows were housed in confinement, had access to free stalls, and were fed a complete ration ad libitum. The total mixed ration (TMR) contained grass hay, alfalfa hay, grass silage, corn silage, corn grain, and various byproduct feeds, depending on availability and cost, and proportioned using a least-cost computation for an average daily production level of 99 lb (45 kg) of 3.5% fat corrected milk. Milking was performed three times per day, beginning at 6 am, 1 pm, and 8 pm.

Blood samples were obtained from the coccygeal vein at 2 hours before, a few minutes before (zero), and at 6, 24, 48, 72, 96, and 144 hours after administration of the corticosteroids, except that 144-hour blood samples were not obtained from the controls. In order to minimize the stress associated with handling and restraint of the cows for venipuncture, blood samples were collected while the cows were resting in free stalls. The first blood samples were obtained between 9:00 and 9:30 am, and the corticosteroids were administered between 11:00 and 11:30 am, immediately after the second blood sample was obtained.

Glucose was measured on the farm immediately after blood collection using a portable analyzer.[c] Blood was also collected in EDTA tubes, and the leukogram was determined by an impedance and optical counter[d] in the laboratory. Blood smears were used for obtaining differential leukocyte counts. Individual cow milk production data was obtained from the farm's automated electronic database.

Statistical Analysis

Parameters measured in this study (blood glucose, total leukocytes, neutrophils, eosinophils, monocytes, lymphocytes, and milk production) were submitted to several analyses of variance, with the objective of determining whether treatment with DEX or PRED was associated with any statistically significant changes in those parameters, and also to determine the times of onset and persistence of any significant effects.

The analysis of variance was done with the PROC MIXED from SAS[19] using the following mixed linear model: $Y = X\beta + Z\gamma + \varepsilon$.

In this model, Y is a vector of the parameter analysed (glucose, total leukocytes, neutrophils, eosinophils, monocytes, lymphocytes, and milk production), b is a vector of fixed effects, y is a vector of unknown random effects, and e is a vector of residual effects. X and Z are matrices of known incidence for fixed effects and random effects, respectively. The effect of the cow was considered a random effect, while the effects of treatment, time and their respective interaction, were considered to be fixed effects. After that, the means and minimal squares (least square means) of all the parameters for each combination treatment*time were calculated, as well as the differences between these means and the respective t-test.

For each parameter studied, values from DEX and PRED-treated cows were compared with those obtained at the corresponding sampling time from the control cows, except that comparisons with the controls were not performed on samples obtained at 144 hours post-administration. Instead, the 144-hour values from the DEX and PRED groups were compared with pre-treatment control group values, by pooling their combined -2 hour and zero-hour values. In addition, values obtained from DEX and PRED-treated groups during corresponding time periods were compared directly with each other.

With two exceptions, no statistically significant differences were found in any of the comparisons made between the three treatment groups with respect to samples obtained and data collected during the pre-treatment period (-2 hours and zero hours). In the first exception, at -2 hours, eosinophil values from the DEX group were significantly greater than those from both PRED and control groups. Although eosinophil values from the DEX group were significantly elevated, they were within the reference range (Figure 4), and two hours later, were no longer significantly elevated. One could speculate than one or more DEX cows might have been briefly exposed to an allergen to which they were mildly sensitized. In the second exception, at –1 day, milk yield was significantly lower in the PRED group than in the control group.

Results

Both DEX and PRED caused significant increases in blood glucose values (Figure 1). The highest values occurred at 24 hours post-administration in the cows treated with DEX. DEX caused blood glucose values to be significantly elevated from six hours through 96 hours. Blood glucose values in DEX-treated cows were significantly higher than in PRED-treated cows at 24, 48, and 144 hours. PRED caused a significant elevation in blood glucose values only at 24 hours.

DEX caused significant increases in total blood leukocyte values at six and 24 hours post-administration, with peak total leukocyte values occurring at 24 hours (Figure 2). PRED did not have any significant effect on total leukocyte counts. DEX-treated cows had significantly higher leukocyte values than PRED-treated cows at 24 hours post-treatment.

DEX caused significant, marked neutrophilia from six hours through 72 hours post-administration, with blood neutrophil values peaking at 24 hours (Figure 3). PRED caused significant neutrophilia only at six hours post-administration. DEX-treated cows had significantly higher neutrophil values than PRED-treated cows at 24 and 48 hours.

Both DEX and PRED caused significant reductions in blood eosinophil values at 48 hours post-administration (Figure 4).

DEX caused significant elevations in blood monocyte values at six and 48 hours post-administration. PRED caused a significant elevation in blood monocyte values only at 24 hours, at which time monocyte values were significantly higher in PRED cows than in DEX cows (Figure 5).

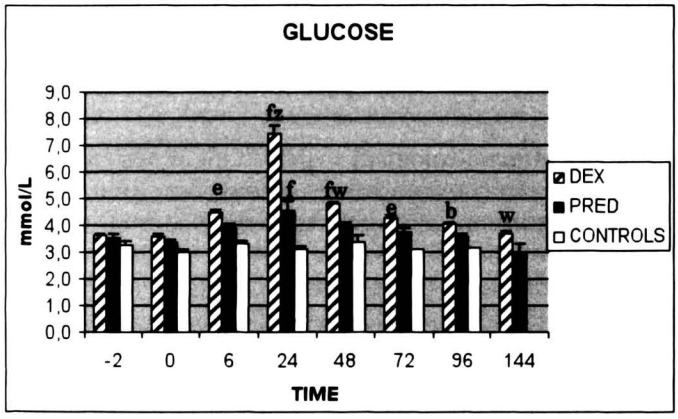

Figure 1. Effects of administration of DEX and PRED on blood glucose values in Holstein cows. Results are expressed as the mean ± standard error. (Reference values: 1.9 – 3.9 mmol/L, Smith[21].) $^{b}P < 0.01$, $^{e}P < 0.0005$, $^{f}P < 0.0001$, when compared with control values; $^{w}P < 0.05$, $^{z}P < 0.0001$, when DEX is compared with PRED.

DEX induced significant reductions in blood lymphocyte counts at 48 and 96 hours post-administration, while PRED induced significant lymphopenia at 6, 24, 48, 96, and 144 hours (Figure 6).

DEX caused a significant, marked drop in milk production on days 1, 2, and 6 post-administration (Figure 7). The magnitude of this reduction was approximately 29% on day 1, 18% on day 2, and 21% on day 6. PRED did not have any significant effect on milk production (Figure 7).

Results obtained from administration of DEX and PRED to lactating Holstein cows are summarized in Table 1.

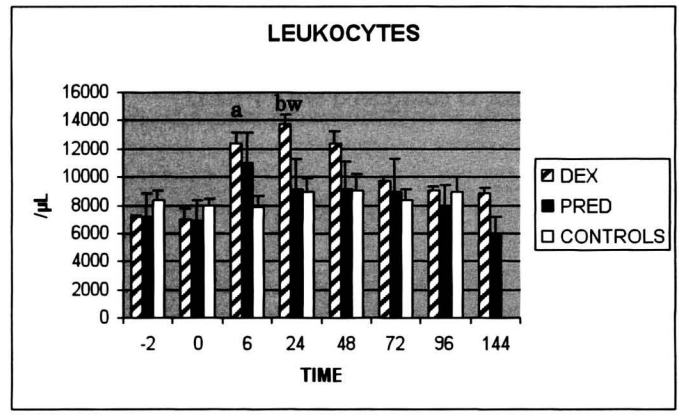

Figure 2. Effects of administration of DEX and PRED on total blood leukocyte values in Holstein cows. Results are expressed as the mean ± standard error. (Reference values: 4,000 – 12,000/µl, Smith[21].) $^{a}P < 0.05$ and $^{b}P < 0.01$ when compared with control values; $^{w}P < 0.05$ when DEX is compared with PRED.

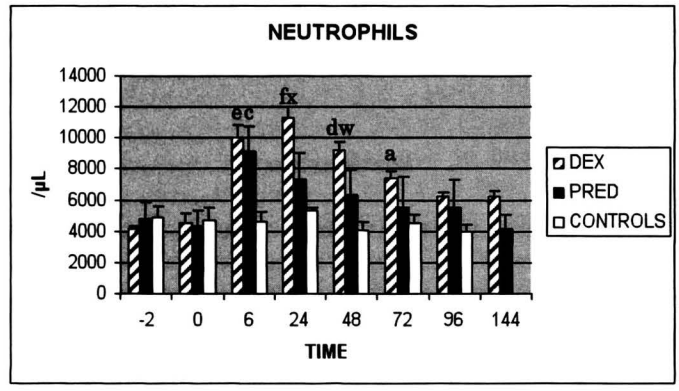

Figure 3. Effects of administration of DEX and PRED on blood neutrophil values in Holstein cows. Results are expressed as the mean ± standard error. (Reference values: 600 – 4000/µl, Smith[21].) $^{a}P < 0.05$, $^{c}P < 0.005$, $^{d}P < 0.001$, $^{e}P < 0.0005$, and $^{f}P < 0.0001$ when compared with control values. $^{w}P < 0.05$ and $^{x}P < 0.01$ when DEX is compared with PRED.

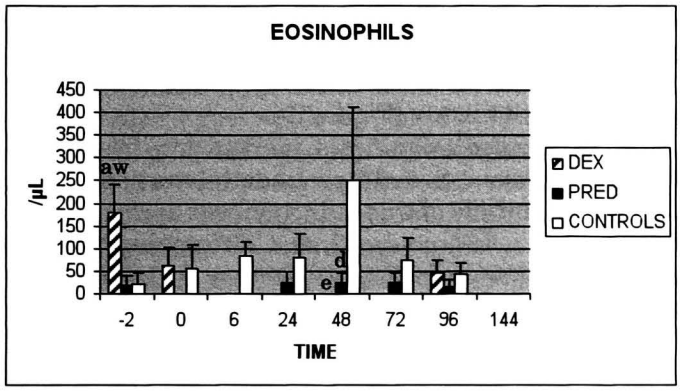

Figure 4. Effects of administration of DEX and PRED on blood eosinophil values in Holstein cows. Results are expressed as the mean ± standard error. (Reference values: 0 – 2,400/µl, Smith[21].) $^{a}P < 0.05$, $^{d}P < 0.001$, and $^{e}P < 0.0005$ when compared with control values. $^{w}P < 0.05$ when DEX is compared with PRED.

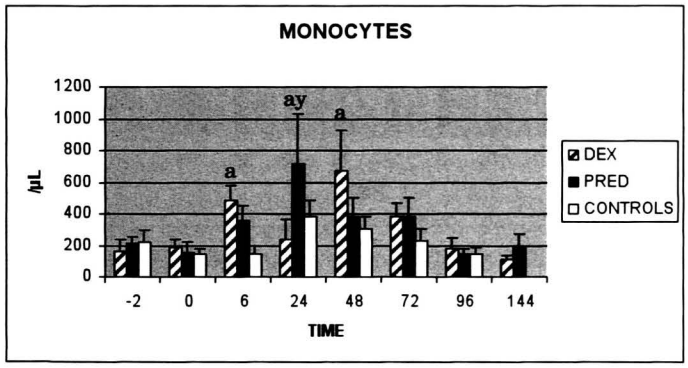

Figure 5. Effects of administration of DEX and PRED on blood monocyte values in Holstein cows. Results are expressed as the mean ± standard error. (Reference values: 25 – 840 /µl, Smith[21].) $^{a}P < 0.05$ when compared with control values; $^{y}P < 0.005$, when DEX is compared with PRED.

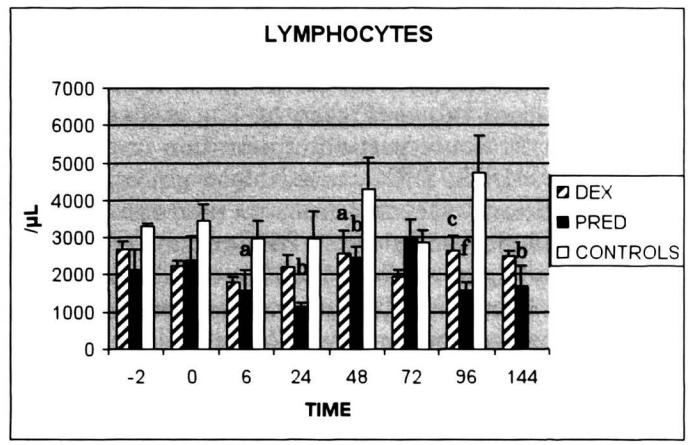

Figure 6. Effects of administration of DEX and PRED on blood lymphocyte values in Holstein cows. Results are expressed as the mean ± standard error. (Reference values: 2,500 – 7,500/µl, Smith[21].) $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.005$, and $^{f}P < 0.0001$ when compared with control values.

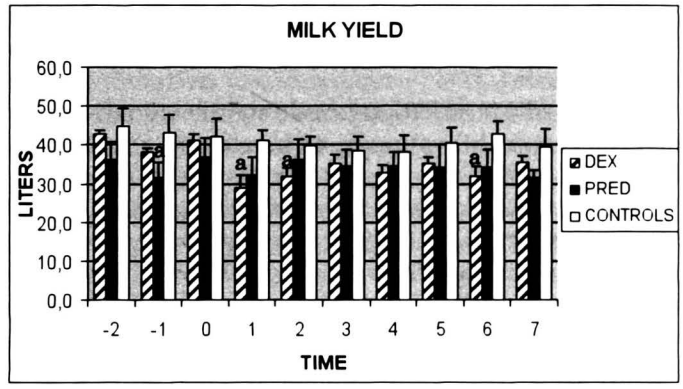

Figure 7. Effects of administration of DEX and PRED on daily milk production in Holstein cows. Results are expressed as the mean ± standard error. $^{a}P < 0.05$ when compared with control values.

Discussion

Problems of cattle for which systemic corticosteroid therapy is most frequently recommended are ketosis and inflammatory processes. Unfortunately, there is not yet a corticosteroid having activity against only one of these two kinds of problems. Apparently, the anti-inflammatory effects and metabolic effects are different aspects of the same process.[15] This has practical ramifications, because the ketotic state in dairy cattle is sometimes secondary to a subacute infectious process, such as metritis or peritonitis. Should a corticosteroid be administered to such cases, the infectious process may be exacerbated[4] or the effectiveness of antimicrobial therapy may be severely compromised.[5]

The pharmacological mechanism of action of corticosteroids in the treatment of ketosis in dairy cattle is not yet fully understood. According to McDonald,[15] corticosteroids cause both an increase in gluconeogenesis and a decrease in peripheral utilization of glucose. According to Herdt and Emery,[11] glucocorticoids induce hyperglycemia in both healthy and ketotic ruminants. The mechanism by which this hyperglycemia is induced may be different in ruminants than in monogastric animals. So far, available evidence suggests that corticosteroids induce a hyperglycemia in ruminants by changing glucose distribution, rather than by increasing the rate of gluconeogenesis. This conclusion is supported by research showing that glucocorticoid therapy in cattle and sheep does not result in a negative

Table 1. Summary of the effects of administration of DEX[a] and PRED[b] on glucose, leukocyte values, and milk yield in lactating Holstein dairy cows.

Parameter measured	DEX	PRED
Hyperglycemia	At 6 through 96 hours	At 24 hours
Leukocytosis	At 6 and 24 hours	None
Neutrophilia	At 6 through 72 hours	At 6 hours
Eosinopenia	At 48 hours	At 48 hours
Monocytosis	At 6 and 48 hours	At 24 hours
Lymphopenia	At 48 and 96 hours	At 6, 24, 48, 96, and 144 hours
Milk production decrease	During days 1, 2, and 6	None

[a]DEX is dexamethasone sodium phosphate and dexamethasone phenyl propionate.
[b]PRED is prednisolone acetate.

nitrogen balance, or cause an increase in the enzymes of gluconeogenesis.[11]

Several studies have shown that glucocorticoids decrease milk production in healthy dairy cows.[1,4,10,26] In addition, a correlation was found between the magnitude of the drop in milk production and the induced hyperglycemia. A tentative conclusion was reached that a reduction in the utilization of glucose for synthesis of lactose may be, at least in part, responsible for the increase in the blood levels of glucose.[11] Recently however, two different groups of researchers have reported that administration of a single dose of dexamethasone-21-isonicotinate to healthy dairy cattle during the second week of lactation did not significantly affect milk production, even though blood glucose values were significantly increased. Jorritsma *et al*[12] studied calving heifers, and Furll and Jackel[7] studied very high producing cows.

It has been shown in ketotic dairy cattle that an increase in blood glucose levels is associated with a decrease in blood ketone bodies.[4,26] This suggests that in bovine ketosis the beneficial effect of corticosteroid treatment might be a result of increased blood glucose concentration, which is then responsible for normalizing the metabolic machinery.[15]

All of the many synthetic corticosteroid compounds currently available for use by clinicians are not universally interchangeable. Different compounds can have different kinds and degrees of activity on target cells, different rates of absorption from injection sites, and different rates of clearance from blood and tissues. As a case in point, Braun *et al*[4] evaluated seven different corticosteroid compounds for their effects on blood glucose levels and milk production in normal and ketotic dairy cows, and for efficacy in treatment of ketosis. Three compounds, flumethasone, dexamethasone, and flumethasone pivalate, produced dramatic increases in blood glucose values in normal lactating cows. One compound (9-fluoroprednisolone acetate) produced moderate blood glucose increases. Prednisone, prednisolone pivalate, and triamcinolone acetonide, produced modest increases.

Peak blood glucose values were achieved within 24 hours following administration of six of these compounds. With the seventh compound (prednisone), peak glucose levels were achieved at 36 hours following administration. Blood glucose values returned to baseline levels by 72 hours following administration of six of these seven compounds. With the seventh compound (prednisone), blood glucose values had not returned to baseline values by the end of the 96-hour observation period.

Flumethasone and dexamethasone produced the most dramatic reductions in milk production in normal cows. Flumethasone pivalate produced moderate reductions, while 9-fluoroprednisolone acetate, prednisone, prednisolone pivalate, and triamcinolone acetonide produced modest reductions. Milk production was most severely depressed on day 1 post-administration with five of these compounds. With the other two compounds (prednisone and triamcinolone acetonide), milk production was most depressed on day 2 post-administration. Following administration of six of these seven compounds, milk production returned to baseline levels on day 3. Milk production had still not returned to baseline levels by the end of the observation period (day 4) following administration of the seventh compound (prednisone). The authors reported that flumethasone and dexamethasone produced the greatest increases in blood glucose values and the greatest decreases in milk production; they were also most efficacious for treatment of ketosis.

Weirda *et al*[26] later conducted a similar study in which dexamethasone di-methyl butyrate and dexamethasone 21-isonicotinate were administered to normal lactating dairy cows. Dexamethasone di-methyl butyrate produced the greatest increases in blood glucose values, with peak values occurring at 72 hours

post-administration, and returning to baseline levels at 96 hours post-administration. With dexamethasone 21-isonicotinate, blood glucose values peaked at 24 hours and returned to baseline levels at 96 hours post-administration. Dexamethasone 21-isonicotinate produced the largest decreases in milk production, and the magnitude of those reductions was similar in both high-producing (>55 lb [25 kg]/day) and low-producing (<55 lb/day) cows. Dexamethasone di-methyl butyrate reduced milk production in high-producing cows, but not in low-producing cows. With both compounds, the greatest decreases in milk production occurred on day 2 post-administration. Milk production returned to baseline levels on day 3 (dexamethasone di-methyl butyrate) or day 4 (dexamethasone 21-isonicotinate) post-administration.

Both compounds were equally effective for treating ketosis in dairy cows, which was somewhat in conflict with Braun *et al*[4] who reported corticosteroid efficacy to be highly correlated with the degree of hyperglycemia produced and the magnitude of milk yield reduction. One could speculate that the capability of dexamethasone 21-isonicotinate to produce longer acting hyperglycemia, and greater and more persistent reductions in milk production, might have compensated for its more modest hyperglycemic effect. However, this explanation finds only modest support from two studies.

Jorritsma *et al*[12] administered dexamethasone-21-isonicotinate to normal dairy heifers in the second week of lactation. Blood glucose values were significantly elevated only on day 2 post-administration, and milk production was not significantly affected. Furll and Jackel[7] administered dexamethasone-21-isonicotinate to normal, very high producing dairy cows in the second week of lactation. Blood glucose values were significantly elevated from day 1 through day 3 post-administration without any significant effect on milk production. Wagner and Apley[23] also observed no effect on milk production following administration of isoflupredone to dairy cows that were recovering from experimental endotoxin-induced mastitis, but did not study the effect on blood glucose. It should be obvious, at this point, that the mechanisms by which glucocorticoid therapy promotes recovery from ketosis in lactating dairy cows are far from adequately understood.

Of the nine corticosteroid compounds that had previously been evaluated in lactating dairy cows (excluding isoflupredone), only prednisone produced as persistent a hyperglycemic effect as DEX did in the present study. However, the degree of hyperglycemia produced by prednisone in that study was characterized as only "modest".[4] Of these same nine compounds, only prednisone caused more persistent suppression of milk production than DEX in this study. However, although the effect of prednisone on milk production was quite persistent, the magnitude of this milk suppression was classified by the authors as "modest".[4]

The product label states that administration of DEX to ketotic cows will increase blood glucose concentrations for seven to eight days (168 to 192 hours). In the present study performed in normal lactating dairy cows, DEX produced a rapid, marked increase in blood glucose values, and hyperglycemia persisted from six hours through 96 hours post-administration. Blood glucose values were not determined between 96 and 144 hours. However, at 144 hours, blood glucose values in DEX cows were significantly higher than in PRED cows, but the controls were not available for comparison. As a substitute for controls, 144-hour blood glucose values from DEX cows were statistically compared with pooled pre-treatment values from control cows, but the difference was not significant.

Possibly, the effects of DEX on blood glucose values actually are more persistent in ketotic cows than in normal cows. Nevertheless, because of the marked and persistent effects of DEX on both blood glucose values and milk production, the authors anticipate that it will prove to be a highly efficacious drug for treatment of ketosis in dairy cows. Parenthetically, it is unlikely that PRED would be a satisfactory treatment for ketosis, because its rather "modest" effect on blood glucose levels occurred only at 24 hours.

Among existing anti-inflammatory drugs, the corticosteroids are some of the most efficient. In this study, changes in the concentrations of some of the formed elements of the blood were used as an indicator of these anti-inflammatory effects.[15] Several different mechanisms of action have been proposed to explain these effects.[13] According to Ferguson and Hoenig,[6] these anti-inflammatory effects result in changes in the concentration, distribution and function of leukocytes, and in inhibition of phospholipase A activity in the plasma membrane of these leukocytes.

Following administration of various corticosteroids to various species of domestic animals, the following changes in the leukogram have been observed: neutrophilia, without a left shift (no increase in numbers of immature neutrophils); eosinopenia; monocytosis in the dog and occasionally in the cat,[14,15] and lymphopenia.

The mechanisms involved in the mediation of these changes in the leukogram are as follows:[14] neutrophilia results from a combination of a) decreased migration of circulating neutrophils into peripheral tissues, and b) increased release of neutrophils into the blood stream from the bone marrow. Lymphopenia results from a) increased migration of circulating lymphocytes into lymphoid tissues and/or bone marrow, and b) temporary sequestration in these locations. Eosinopenia results from a combination of a) sequestration of eosinophils in tissues, and b) inhibition of their release from the bone

marrow. Monocytosis may be caused by mobilization of marginated cells within the blood vasculature.

Veterinary textbooks usually summarize the effects of corticosteroid therapy on the leukogram of animals as follows: The peak response occurs from four to eight hours following administration. Values then return to reference ranges within 24 hours following a single injection of a short acting corticosteroid. Following long-term therapy, where the corticosteroid is injected daily for 10 or more days, values return to reference ranges with two to three days.[14,25] These summary statements do not specify the corticosteroid compounds used or the animal species in which the studies were conducted. Our study and others[7,8,22] demonstrate that this definition does not adequately describe the effects of modern corticosteroid compounds on the leukogram of cattle.

In our study, the effects of both corticosteroids on lymphocyte counts were somewhat surprising in that PRED caused lymphopenia at 6, 24, 48, and 96 hours, while DEX caused lymphopenia only at 48 and 96 hours. This was the only parameter studied in which the effects of PRED were more marked than those of DEX.

Another unexpected observation was made during this study. Prior to administration of either corticosteroid, blood neutrophil concentrations were always higher than blood lymphocyte concentrations, both in the principals and in the controls. This finding is the reverse of what is stated in most hematology textbooks. The authors do not believe that this could have been a result of any stress associated with sample collection since a great deal of effort was made to minimize this stress. In addition, there is always a significant time lag (at least four hours) between application of a stress to an animal and the appearance of neutrophilia and lymphopenia in the animal's hemogram.[14]

Most textbooks state that administration of corticosteroids to animals will produce lymphopenia. However, three groups of workers recently reported that blood lymphocyte values were not significantly affected by administration of a single dose of a corticosteroid to cattle. Furll and Jackel[7] and Thanasak *et al*[22] administered dexamethasone-21-isonicotinate to normal high producing dairy cattle in the second week of lactation. Bednarek *et al*[3] administered flumethasone to calves with an experimentally induced, noninfectious, lung inflammation model. Either not all corticosteroid compounds are capable of eliciting lymphopenia, or not all corticosteroids are capable of eliciting lymphopenia in all species. It is also possible that changes in lymphocyte values might have been observed in these three studies if higher dosages and/or repeated injections had been utilized.

According to Roth and Kaeberle[17] there are marked species differences in the response of circulating lymphocytes to glucocorticoid hormone administration. Compared with the corticosteroid-sensitive species, such as hamsters, mice, rats, and rabbits, glucocorticoid-induced lymphopenia in cattle is not as easily induced or as profound.

Although glucocorticoid-induced monocytosis has been described in the dog and cat,[14,15] the effect of glucocorticoids on bovine monocyte kinetics is not so well understood.[17] In our study, significant increases in blood monocyte values occurred at 24 hours following administration of PRED and at six and 48 hours after the administration of DEX. Schalm *et al*[20] first reported glucorticoid-induced monocytosis in dairy cows following treatment with 9-floroprednisolone. Administration of adrenocorticotropic hormone to normal cattle did not result in any changes in the numbers of circulating monocytes.[16]

Conclusions

Because DEX produced more dramatic and persistent changes in blood glucose values and milk production than did PRED, the authors believe that DEX is likely to be more efficacious than PRED for treating ketosis in dairy cows. Because DEX produced more dramatic and persistent effects on blood neutrophil values than PRED, it is also likely to be a better option for use as an anti-inflammatory drug.

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Endnotes

[a]Dexafort – Intervet Portugal-Saúde Animal, 2725-397 Mem Martins/Portugal

[b]Hostacortina – Intervet Portugal-Saúde Animal, 2725-397Mem Martins/Portugal

[c]i-Stat, Sensor Devices Incorporated, Waukesha, WI, USA

[d]Cell Dyn 3700, Abbott Diagnostic Division, Abbott Park, IL, USA

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