Long-Term Evaluation of a Prolonged-Release Formulation of N-Methionyl Bovine Somatotropin in Lactating Dairy Cows[1,2]

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ABSTRACT

Eighty Holstein cows (first, second, or third lactation) were used to evaluate the efficacy of a prolonged-release formulation for sometribove (n-methionyl bovine somatotropin). Cows were fed ad libitum a complete mixed diet and milked twice daily. Cows were allocated randomly by parity to two treatment groups receiving 500 mg sometribove in a prolonged release formulation or excipient at 14-d intervals starting at 60 ± 3 d postpartum and continuing for 36 wk. Treatment with sometribove increased FCM yield to a similar extent (11.4%, +3.1 kg/d) in primiparous and multiparous animals. Milk content of lactose, fat, ash, and Ca was not affected, but protein and phosphorous were slightly greater (<5%) in milk from sometribove-treated cows. Within a 14-d injection interval, animals treated with sometribove displayed a cyclic pattern in milk yield, but a similar pattern was not evident in feed intake. Protein and fat percentages in milk were higher the 2nd wk of the injection cycle (6 and 4%, respectively) and this difference appears unrelated to nutrient balance. Over the treatment period (252 d), sometribove-treated animals increased voluntary feed intake to a sufficient extent so that body weight gains, net energy balance, and body condition scores did not differ between treatment groups. Gross lactational efficiency (milk per unit of feed) was improved in sometribove-treated cows, and no adverse health effects were observed. Results demonstrate that bovine somatotropin administered by a prolonged-release formulation is effective in improving milk yield and productive efficiency.

INTRODUCTION

In 1937, Asimov and Krouze (1) first demonstrated that injections of crude pituitary extracts increased milk production in dairy cows. Aspects of this were examined in the subsequent 40 yr. Particularly noteworthy were a series of short-term investigations in the 1940s by scientists at the National Institute for Research in Dairying (28), who first demonstrated that the galactopoietic effect of pituitary extracts was due to the somatotropin fraction, and the studies of Brumby and Hancock (9) and Machlin et al. (17), which demonstrated over 40% increases in milk yield with longer treatments (10 to 12 wk). All these earlier investigations utilized low producing dairy cows [see reviews (15, 20)]. The prevailing theory of somatotropin's action was as an acute effector primarily in-

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creasing lipid mobilization and blood concentrations of glucose (10, 16, 29). Thus, improvements in efficiency would be expected in low producing cows treated with somatotropin, but acute metabolic disorders from excessive mobilization of body fat were anticipated if high producing cows were used (16).

In 1980, Bauman and Currie (3) postulated a different mechanism of action when they proposed that somatotropin was a homeorhetic control rather than a homeostatic effector. A series of investigations in the last decade have confirmed that somatotropin is a chronic regulator, which results in an exquisite coordination of metabolic processes so that more nutrients are partitioned toward milk synthesis during lactation and toward lean tissue accretion during growth [see reviews (5, 8, 20)]. In addition, longer term studies (22 to 38 wk of treatment) have demonstrated that the milk yield response to exogenous somatotropin (pituitary-derived or recombinantly derived) persists in high producing dairy cows with no apparent adverse health effects (4, 11, 22, 24).

Studies that have examined the biology of the animal's response to somatotropin traditionally have involved daily injections (subcutaneous or intramuscular) of exogenous hormone. The objective of our investigation was to examine the response to a prolonged-release formulation of bovine somatotropin in lactating cows. This formulation was administered at 14-d intervals beginning after peak milk production and continuing throughout lactation.

MATERIALS AND METHODS

Animals and Treatments

Eighty Holstein cows (24 first, 46 second, and 10 third lactation; no previous somatotropin treatment) from the dairy herd at Cornell University were used for this study. Half of the cows within each lactation group were assigned randomly to one of two treatments. Beginning at 60 ± 3 d postpartum, cows received 1.3 ml of either a prolonged-release formulation containing 500 mg of n-methionyl bovine somatotropin (bST; sometribove,[5] provided by Monsanto Agricultural Co.) or a similar volume of excipient (placebo control). Treatments were administered at 14-d intervals (injection interval) by intramuscular injection (16-gauge needle) in one of four alternating sites (upper or lower, right or left posterior semitendinosus muscle). Cows were treated until dry off or until the completion of 25 injection cycles (410 ± 3 d postpartum).

Four cows started and then were removed from the study. Two of these cows (1 control and 1 bST treatment) were removed because they were diagnosed as having Johnes disease (confirmed at necropsy) after approximately 2 mo on treatment. This disease is endemic in the Cornell University herd. The other two cows (1 each treatment) were misinjected (incorrect injection interval) after approximately 1 mo on treatment. Because the incidents for these 4 cows occurred prior to completing the assignment of all 80 cows to the study, they were replaced at random with other available animals. An additional cow (control treatment) had a physical injury and was excluded from the data set. Thus, a total of 79 cows completed the study.

General Procedures and Measurements

After parturition, cows were moved to a tie stall barn and housed in individual stalls throughout the study. Cows remained in the tie stalls except for twice-daily trips to the milking parlor at approximately 1200 h and 2400 h. The unit had artificial lighting [approximately 258 lx (14 h/d) to 54 lx (10 h/d) at shoulder height of the cows] and automatic ventilation.

Cows were fed ad libitum one of three total mixed diets (Table 1). Orts were recorded and fresh feed offered once daily (1000 h). The three diets were formulated to meet or exceed the nutrient requirements for 37, 27, and 20 kg/d milk production. For the first 90 d postpartum, all cows were offered the high energy, high protein diet. Thereafter, cows were switched to lower energy and protein diets according to milk yield and body condition. The decision to shift diets was conservative in terms of milk yield and body condition so that lactational performance would not be compromised. For milk, dietary shifts were made when yield for

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[5] Sometribove is the nonproprietary name for n-methionyl bovine somatotropin established by US Adopted Names Program in accordance with the Federal Food, Drug and Cosmetic Act (14).

each day in the previous 2-wk injection interval was less than 27 kg (shift from high to medium) or 19 kg (shift from medium to low). Weekly feed samples (individual ingredients and total mixed diets) were composited at monthly intervals and analyzed by the New York Dairy Herd Improvement Cooperative (Forage Testing Laboratory, Ithaca, NY).

Milk yield was recorded at each milking (twice daily). From 1 wk postpartum, a.m. and p.m. milk samples were collected 1 d each week (d 5 and d 12 of each injection interval) and analyzed by infrared techniques for milk fat, protein, and SCC (2). Lactose was determined by enzymatic analysis (12). Milk samples were obtained for Ca, P, and total ash analyses at 1 and 2 wk prior to start of treatment and at 4-wk intervals during treatment. Lyophilized milk samples were heated at 500°C for 16 to 20 h for ash determinations. The ashed sample was then solubilized in 5% nitric acid for mineral determinations. Inductively coupled argon plasma emission spectrophotometry (Perkin Elmer Plasma II ICP, Perkin Elmer Corp., Norwalk, CT) was used for analysis of Ca (317.933 nm line) and P (213.618 nm line).

Body weights were determined after the p.m. milking on 2 consecutive d biweekly throughout lactation. Because determinations were biweekly for all cows, this represented d 14/1 or d 7/8 of the injection interval depending on the week that treatment was initiated. Net energy (NE) balance was calculated weekly. Calculation of NE intake utilized NE values for individual feed ingredients. Milk energy was calculated using average weekly milk yield and percent fat

TABLE 1. Composition of the complete mixed diets.

	Diets		
Ingredients and nutrients[1]	High energy and protein	Medium energy and protein	Low energy and protein
Ingredient[2]			
Hay crop silage, %	13.5	25.5	39.9
Corn silage, %	41.0	35.5	39.9
High moisture shell corn, %	27.5	26.6	15.4
Soybean meal (dehull), %	14.3	9.9	3.3
Nutrient content			
Net energy lactation,[3] Mcal/kg	1.63	1.56	1.44
Crude protein, %	17.6	15.4	14.2
Acid detergent fiber, %	19.1	22.3	26.6
Calcium, %	.90	.88	.78
Phosphorus, %	.52	.47	.44
Magnesium, %	.42	.42	.38
Potassium, %	1.18	1.22	1.33
Sodium, %	.37	.38	.27
Sulfur, %	.33	.28	.26
Iron, ppm	399	413	441
Copper, ppm	14	16	15
Manganese, ppm	75	81	76
Zinc, ppm	89	93	78
Vitamin A, 1000 IU/kg[4]	4.9	4.3	3.6
Vitamin D, 1000 IU/kg[4]	2.2	2.0	1.6

[1] Expressed on a 100% dry matter basis.

[2] In addition, sodium sesquicarbonate (.70, .70, 0.35%), magnesium oxide (.30, .30, .15%), trace-mineralized salt (.4, .4, .4%), were included in the high, medium, and low energy and protein diets, respectively. All formulations contained mineral and vitamin supplements as needed to meet National Research Council recommendations (19).

[3] Net energy values were calculated from individual ingredient values.

[4] Supplemented amounts.

according to NRC (19). Net energy for maintenance was according to NRC (19) using a 4-wk rolling average for body weight.

A general physical examination (blind to treatment assignment) was performed on all cows at 40 ± 3 and 180 ± 3 d postpartum and again during the last injection cycle prior to dry off. During these examinations, blood samples were obtained for clinical chemistry profiles (11), and body condition was scored (27). Additionally, animals were observed daily for general health status and abnormalities recorded.

Reproductive management was according to standard practices for the resident herd with all personnel involved being blind to treatments. Reproductive examinations of all cows were performed at 4 to 5-wk postpartum, and animals were checked for signs of estrus a minimum of three times daily. Cows were bred by artificial insemination at the first observed estrus after 50 d postpartum. If deemed appropriate by the veterinary clinicians, cows remaining anestrus by 75 to 80 d postpartum were bred following estrus synchronization (prostaglandin $F_{2\alpha}$). Cows that failed to conceive by 190 d postpartum were considered open. Animals were dried off when milk yield (averaged over a 2-wk interval) fell below 9.1 kg/d or at 60 ± 3 d prior to expected date of parturition. Open cows remained in the study until dried off for low milk production or until 410 ± 3 d postpartum.

Statistics

Statistical analyses were conducted using Statistical Analysis System (25). Quantitative variables were analyzed using the linear model, $Y_{ijk} = \mu + T_i + L_j + TL_{ij} + \beta PRE_{ijk} + e_{ijk}$, where μ = overall mean; T_i = treatment effect; L_j = lactation (primiparous vs. multiparous) effect; TL_{ij} = treatment × lactation interaction; PRE_{ijk} = covariate; β = regression coefficient for PRE_{ijk}; and e_{ijk} = residual. Body weight and variables used in gross efficiency calculations were not adjusted covariately. For each measure of efficacy, analyses were performed on the average daily value over 18 injection cycles (252 d). Corrected feed efficiency and 3.5% FCM data for cows not completing 18 injection intervals because of early pregnancy (≤84 ± 3 d postpartum) were extrapolated to 252 d of treatment using linear regression of averages of the last 6 completed injection intervals. Efficacy data for animals that dried off early due to low milk production (i.e., >60 ± 3 d prepartum) were not extrapolated.

RESULTS

Prior to treatment, milk yields for each treatment group were similar within parity groups (14-d pretreatment least squares mean: 28.6 kg/d primiparous; 37.6 kg/d multiparous) although in the primiparous cows, the group assigned to the bST treatment had slightly lower milk production than the controls (27.7 vs. 29.4 kg/d, $P > .05$). Treatment with bST increased milk yield and FCM yield by a similar magnitude in primiparous and multiparous cows (Table 2). Over the 18 injection intervals (252 d of treatment), yields of milk and FCM were increased by 2.8 (10.4%) and 3.1 kg/d (11.4%), respectively. Fat, lactose, ash, and Ca composition of milk was not affected by treatment (Table 2). Protein content was slightly higher (3%) in animals receiving bST and a similar increase occurred for milk phosphorus content (Table 2).

The temporal patterns of the response in milk yield are shown in Figure 1. There was an immediate response to the first injection, and thereafter the difference in milk yield tended to

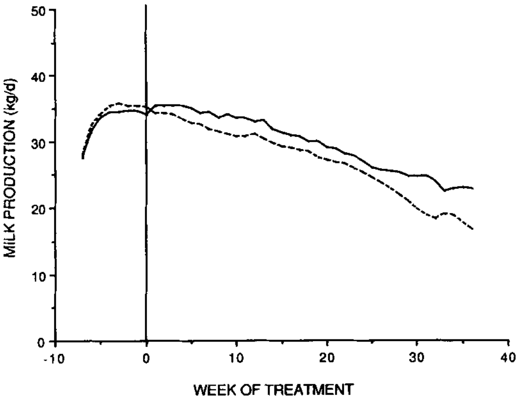

Figure 1. Temporal pattern of milk production. Treatments were initiated at time zero (60 ± 3 d postpartum) and involved intramuscular injection of a prolonged release formulation of 500 mg sometribove (solid line; n = 40 cows) or excipient (dashed line; n = 39 cows) at 14-d intervals. Values used in constructing curves were weekly averages.

TABLE 2. Effect of treatment with a prolonged release formulation of sometribove (bST) on yield and composition of milk.

Variable[1]	Control						bST					
	Primiparous		Multiparous		Overall		Primiparous		Multiparous		Overall	
Cows, n	12		27		39		12		28		40	
	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE
Milk, kg/d	25.3^a	.65	28.2^a	.44	26.8^a	.39	28.0^b	.65	31.1^b	.43	29.5^b	.39
3.5% FCM, kg/d	25.9^a	.67	28.7^a	.45	27.3^a	.41	28.7^b	.67	32.2^b	.44	30.4^b	.40
Fat, %	3.68	.092	3.68	.061	3.68	.055	3.74	.092	3.79	.060	3.77	.055
Protein, %	3.20	.037	3.30^a	.025	3.25^a	.022	3.28	.037	3.39^b	.024	3.34^b	.022
Lactose, %	4.80	.029	4.72	.019	4.76	.018	4.80	.029	4.75	.019	4.77	.018
Ash, %	.73	.007	.73	.005	.73	.004	.73	.007	.74	.005	.74	.004
Calcium, ppm	1101	22.7	1090	15.1	1096	13.6	1104	22.7	1117	14.9	1110	13.5
Phosphorus, ppm	887	17.3	848^a	11.6	867^a	10.4	917	17.3	902^b	11.4	910^b	10.4

[a,b] For each variable, means within a lactation number with different superscripts differ ($P<.05$).

[1] Treatment period was 252 d commencing at 60 ± 3 d postpartum. Results represent least squares means (±SE of least squares means) adjusted for pretreatment values. Milk and FCM yields were obtained at each milking; fat, protein, and lactose were analyzed in a.m. and p.m. samples obtained once per week; ash, calcium, and phosphorus were analyzed in a.m. and p.m. samples obtained every 4 wk.

gradually increase as lactation progressed due primarily to the declining milk yield of the controls. Milk yields shown in Figure 1 are based on average weekly milk yield. Within an injection invertal, the pattern of milk yield was cyclic and nearly indentical for each of the 18 injection intervals. The composite of the 18 injection intervals is shown in Figure 2. This pattern consisted of a progressive increase over d 1 to 7, and a progressive decrease in milk yield during d 9 to 14 of the injection interval.

Milk composition was only determined 1 d/wk (d 5 and 12 of each injection interval), so a comprehensive comparison with the pattern of milk yield within an injection cycle was not possible. However, examination across the treatment period indicated that a cyclic pattern within each injection interval occurred for some milk components (see Figure 3). Although the magnitude is small, a higher value for milk protein percentage was observed consistently for the 2nd wk of the injection interval (6%; $P<.05$). This peak and valley pattern also was apparent for milk fat percent although not as consistent as for milk protein. In contrast, the percentage of lactose was relatively constant and not affected by week of injection interval.

Dry matter intake was increased with bST treatment when expressed as kg/d or as a per-

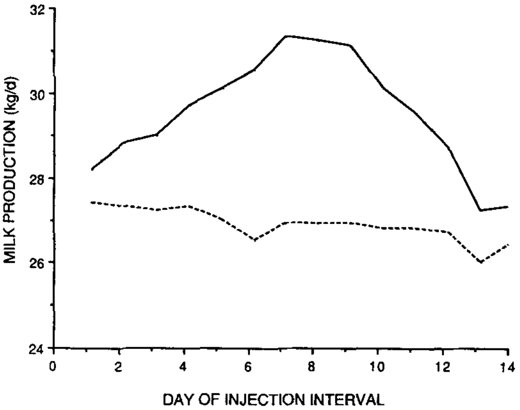

Figure 2. Pattern of milk yield by day within an injection interval. An intramuscular injection of a prolonged release formulation of 500 mg sometribove (solid line; n = 40 cows) or excipient (dashed line; n = 39 cows) was administered at 14-d intervals. Values represent the average across 18 injection intervals. Standard deviation averaged 1.8 kg for controls and 1.4 kg for sometribove-treated cows.

cent of body weight (Table 3). There was no evidence of a cyclic pattern for feed intake within an injection cycle. The pattern across the treatment period was a gradual increase in voluntary intake over the first 10 wk for cows on bST treatment. Thus, bST treatment resulted in increases in both net energy intake and milk energy secretion (Table 3).

Cows in both treatment groups were in a slight negative energy balance immediately preceding treatment (Figure 4). However, there was a greater energy deficit early in the treatment period in the bST cows compared with controls. At the onset of bST treatment, energy balance declined sharply due to increased milk yield without an immediate compensatory increase in feed intake. As voluntary intake increased, energy balance gradually increased, becoming positive by approximately wk 7 of treatment. During the last third of the treatment period, cows treated with bST had a positive energy balance that was greater than controls (Figure 4).

Over the entire treatment period, average NE balance and body weight gain were similar for control and bST groups (Table 3). Body condition scores were consistent with the energy balance and weight gain data. Condition scores were lower (*P*<.05) in bST-treated animals at 180 d postpartum (120 d of treatment) but did not differ at the end of the treatment period (Table 3). Over the treatment period, bST administration increased (*P*<.05) apparent feed efficiency (Table 3). Gross efficiency, both observed and corrected for body weight changes, also was improved (*P*<.05) in the bST-treated group.

Animals were in good health throughout the study. Conception rates and calving rates were similar for both treatment groups (85 and 83% for control and bST groups, respectively). No incidences of catastrophic health effects, such as ketosis or milk fever, were observed; this is consistent with previous reports (4, 11, 22, 24). Eppard et al. (11) emphasized that examination for subtle health effects of bST requires large

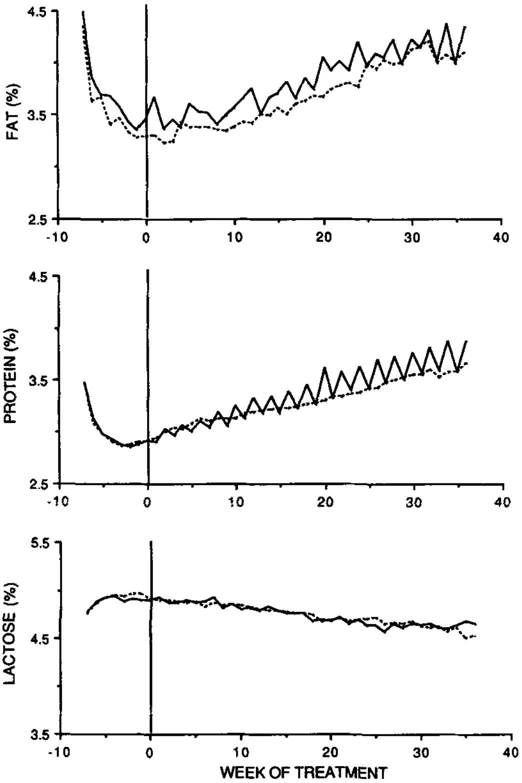

Figure 3. Temporal pattern of milk fat, protein, and lactose percentages. Treatments were initiated at time zero (60 ± 3 d postpartum) and involved intramuscular injection of a prolonged release formulation of 500 mg sometribove (solid line; n = 40 cows) or excipient (dashed line; n = 39 cows) at 14-d intervals. Values are averages of a.m. and p.m. samples obtained once per week.

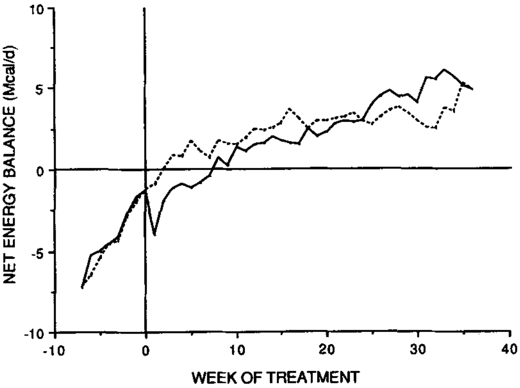

Figure 4. Temporal pattern of net energy balance. Treatments were initiated at time zero (60 ± 3 d postpartum) and involved intramuscular injection of a prolonged release formulation of 500 mg sometribove (solid line; n = 40 cows) or excipient (dashed line; n = 39 cows) at 14-d intervals. Values used in constructing curves were weekly averages.

TABLE 3. Effect of treatment with sometribove (bST) on intake and energy-related variables.

Variable[1]	Control						bST					
	Primiparous		Multiparous		Overall		Primiparous		Multiparous		Overall	
	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE	$\overline{X}$	SE
Dry matter intake,												
kg/d	17.4	.36	20.3^{a}	.24	18.8^{a}	.21	18.3	.36	21.0^{b}	.23	19.6^{b}	.21
% body weight	3.2^{a}	.07	3.4^{a}	.05	3.3^{a}	.04	3.4^{b}	.07	3.6^{b}	.04	3.5^{b}	.04
Net energy intake, Mcal/d	27.7^{a}	.61	32.6^{a}	.41	30.2^{a}	.37	29.5^{b}	.61	34.1^{b}	.40	31.8^{b}	.37
Milk energy secretion, Mcal/d	17.8^{a}	.46	19.8^{a}	.30	18.8^{a}	.27	19.7^{b}	.46	22.1^{b}	.30	20.9^{b}	.27
Net energy balance, Mcal/d	.8	.46	3.1	.30	1.9	.27	1.0	.46	2.5	.30	1.7	.27
Body weight gain, kg/d	.4	.04	.5	.03	.5	.02	.4	.04	.4	.03	.4	.02
Body condition scores[2]												
Pretreatment	2.9	.12	2.9	.08	2.9	.07	3.0	.12	2.7	.08	2.9	.07
Midtreatment	3.3^{a}	.12	3.2^{a}	.08	3.2^{a}	.07	2.8^{b}	.12	2.8^{b}	.08	2.8^{b}	.07
End of treatment	3.3	.12	3.4	.08	3.3	.07	3.1	.08	3.2	.08	3.2	.07
Apparent feed efficiency, FCM/dry matter intake	1.56	.034	1.44^{a}	.022	1.50^{a}	.021	1.61	.034	1.59^{b}	.022	1.60^{b}	.020
Gross efficiency, kg FCM/Mcal net energy intake												
Observed	.98	.020	.90^{a}	.013	.94^{a}	.012	1.00	.020	.98^{b}	.013	.99^{b}	.012
Corrected[3]	1.01	.015	.95^{a}	.010	.98^{a}	.009	1.04	.015	1.01^{b}	.010	1.03^{b}	.009

[a,b] For each variable, means within a lactation number with different superscripts differ ($P<.05$).

[1] Treatment period was 252 d commencing at 60 ± 3 d postpartum. Results for body condition scores, apparent feed efficiency, and gross efficiency represent actual (unadjusted) means ± SE. All other results represent least square means (±SE of least squares means) adjusted for pretreatment responses.

[2] Body condition was scored at d 40 ± 3 postpartum (pretreatment), d 180 ± 3 postpartum (midtreatment; d 120 ± 3 of treatment), and during the last injection interval (end of treatment).

[3] Corrected for body weight changes by the formula: FCM/[NEI − (5.12 Mcal/kg × BW gain), where FCM = 3.5% FCM (kg/d), NEI = net energy intake (Mcal/d), and BW gain = BW gain (kg/d).

numbers of animals treated under a range of environmental and management conditions. For this reason, health data, including clinical chemistry and reproductive performance, will be published at a later date together with data from several other sites.

DISCUSSION

This study demonstrated the efficacy of a prolonged-release formulation of bST for increasing milk production and productive efficiency of dairy cows. The use of a prolonged-release formulation reduces labor needed for administering treatments as compared to the daily injections, which have been utilized in previous investigations. Primiparous and multiparous cows had similar increases in milk yield over the 252-d treatment period (increases of 2.7 and 2.9 kg/d, respectively) (Table 2). The pattern of response in milk yield across the treatment period (Figure 1) was similar to other long-term studies involving daily injection of bST (4, 9, 17, 22, 24). However, a distinct cyclic pattern in milk yield within each 14-d injection interval was observed consistently across all 18 injection intervals (Figure 2). Because of this cyclic response, milk response to the prolonged-release formulation (10.4% increase) might be less than for a comparable amount of hormone divided into daily injections.

Previous studies have shown a hyperbolic dose-response curve with a pattern of diminishing returns in lactating cows treated with increasing doses of bST (4, 12). Furthermore, milk response was related to average daily concentration of bST in circulation rather than to any particular circulating pattern of bST within a day (13, 18). Blood concentrations of bST were not quantified in this investigation. However, the pattern of milk yield over the first 9 d of an injection interval (Figure 2) was nearly identical to that obtained over the same period following the initiation of daily injections of bST (7, 17, 21). In addition, the progressive decline in milk yield during the last portion of an injection interval (Figure 2) was similar to the pattern of decline observed when daily injections of bST are terminated (7, 17, 21). These data suggest that the prolonged-release formulation we utilized must be providing a diminishing quantity of bST during the last one-third of the injection interval and that this quantity was substantially below the amount needed to maximize milk yield response.

Short-term studies (a few days or weeks in duration) have indicated that treatment of lactating cows with bST does not affect feed intake [see review (20)]. The extra nutrients needed to support the increase in milk yield come from a decrease in tissue synthesis (energy deposition in body reserves) if cows are in positive energy balance (23) or from a mobilization of body reserves if cows are in negative energy balance (6, 26). However, longer term studies involving daily injections of bST have demonstrated that voluntary intake increased after several weeks of treatment (4, 22, 24). This increase in voluntary intake was of sufficient magnitude to meet nutrient needs for the increased milk yield and occurred whether diets consist of only pasture (22) or of high concentrate:forage mixtures (4, 24). We also observed voluntary intake increased in cows treated with the prolonged-release formulation of bST (Table 3) in spite of the cyclic pattern of milk yield within a 2-wk injection interval. The consistency of studies regarding the increase in voluntary intake with bST treatment suggests that tissue requirements for nutrients must play a key role in the chronic regulation of voluntary intake.

Short-term calorimetry studies (23, 26) and theoretical calculations with long-term studies (4, 24) indicate the improvements in productive efficiency that occur with bST treatment are due to a reduction in the proportion of consumed nutrients used for maintenance. Results from this study are consistent with that conclusion. The corrected gross efficiencies (kg FCM/Mcal NE intake; Table 3) are comparable to theoretical values (.98 vs. .97 for controls and 1.03 vs. 1.01 for the bST treatment) as calculated using energy requirements for maintenance and milk (19).

Over the 252-d treatment period, intake was sufficient to allow body reserves to be replenished. The control and bST treatment groups did not differ in average NE balance, body weight gain, or body condition score (Table 3). Other long-term studies have demonstrated similar results (4, 22). In contrast, Soderholm et al. (24) observed lower body fat and body condition scores and a trend toward lower body weight gain with increasing dose of bST. A logical explanation for the difference in their study is that all cows were fed ad libitum the same high energy diet throughout lactation (24). Thus, lower producing cows (e.g., the control group) would tend to be fatter than normal and overconditioned at dry off.

The small, consistent sawtooth response we observed in milk protein percentage was unexpected (Figure 3). Previous studies using daily injections of bST observed a decrease in protein content of milk if production responses caused cows to be in negative nitrogen balance [see review (20)]. We observed that milk protein content for the bST treatment group was similar to controls for wk 1 of the injection interval (3.23 vs. 3.25%), but the wk 2 value was 6% greater ($P<.0001$). Thus, protein content was greater the 2nd wk of the injection interval when milk yield averaged 5% less than the sampling day for wk 1 (compare d 5 and 12 in Figure 2). In addition, the pattern in protein content would oscillate below values for control cows if protein supply were limiting. We observed the opposite; oscillation was greater than the protein content of controls. This sawtooth response was observed consistently throughout the treatment period, whereas nutrient supply would have been limiting only in the first few weeks of treatment (prior to the increase in voluntary intake). Therefore, the regular peak and valley pattern in milk protein content would not appear to be related to nutrient balance.

Previous studies have demonstrated that the fat content of milk increases with bST treatment if milk responses are of sufficient magnitude to cause cows to be in a negative energy balance (20). Our results are consistent with this over the first few weeks of treatment (Figure 3, Figure 4). However, cows receiving bST were in positive energy balance over the last 30 wk of treatment, and yet milk fat content had a sawtooth pattern. This pattern was less pronounced than that observed for milk protein. Over the period of the study when bST-treated cows were in positive NE balance (injection intervals 4 to 18), milk fat content averaged 4% more in wk 2 of the injection interval as compared with wk 1 ($P<.10$). For the reasons previously discussed, this pattern would not appear to be related to nutrient supply.

The basis for the sawtooth pattern in milk protein and fat content that occurred when cows were treated with the prolonged-release formulation of bST is unknown. Studies involving more frequent sampling over an injection interval, to establish the temporal pattern for content and yield of milk fatty acids and specific protein components, should provide some insight. One possible explanation relates to the bST-induced changes in mammary metabolism and in other body tissues. If the half-lives of specific changes in the biochemical machinery for processes related to lactose production (supply of glucose and synthesis of lactose) were shorter than for processes related to protein and fat production, then the pattern would be as we observed (Figure 3). In this situation, as bST concentrations declined in the last phase of the injection interval, lactose production would decrease more rapidly than protein and fat production. Given that lactose is the major osmoregulator of milk volume, milk yield would decrease, milk lactose content would be unchanged, and milk content (but not total yield) of protein and fat would increase.

This study confirms the efficacy of a prolonged-release formulation for bST administration to lactating dairy cows. The magnitude of milk response appears to be less than would be expected from a similar quantity of hormone administered by a series of daily injections, and the lessening is due to the cyclical nature of the response. As with other bST studies, improvements in overall milk production efficiency are explained by the reduction in the proportion of nutrients used for maintenance. Additionally, we observed no evidence to suggest that the prolonged-release formulation of bST had any adverse effects on animal health. Observations from this study support the concept that bST administration to lactating cows alters nutrient partitioning in favor of milk production and demonstrate that the animal is able to adapt to the increased demand for nutrients by increasing voluntary intake. Metabolic processes are altered in a coordinated manner such that animal health is not compromised and tissue energy reserves utilized for milk yield in early phase of lactation are replaced by the end of lactation.

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