Effect of Prepartum Propylene Glycol Administration on Periparturient Fatty Liver in Dairy Cows

VAUGHN A. STUDER, RIC R. GRUMMER,[1] and SANDRA J. BERTICS
Department of Dairy Science
University of Wisconsin
Madison 53706

CHRISTOPHER K. REYNOLDS
Ruminant Nutrition Laboratory
US Department of Agriculture, ARS
Beltsville, MD 20705

ABSTRACT

Plasma glucose concentration during late gestation was thought to be important for the development of fatty liver near parturition. Thirteen multiparous cows were given a 1-L oral drench of propylene glycol once daily beginning 10 ± 3.6 d prepartum until parturition. Eleven control cows received a 1-L water drench. Plasma glucose increased following propylene glycol administration. Plasma NEFA concentration was 403 and 234 μM, and plasma insulin concentrations were .354 and .679 ng/ml, for control cows and cows treated with propylene glycol measured from 1 to 7 d prepartum. Plasma NEFA tended to be lower in cows treated with propylene glycol from 1 to 21 d postpartum. Prepartum propylene glycol administration reduced hepatic triglyceride accumulation by 32 and 42% at 1 and 21 d postpartum, respectively. Prepartum plasma BHBA was reduced during propylene glycol administration. Prepartum plasma glucose, NEFA, BHBA, and insulin were strongly correlated with liver triglyceride at 1 d postpartum (r = –.49, .45, .36, and –.49, respectively). Pre- and postpartum DMI were not affected by treatment. Milk production and composition measured through 21 d postpartum were not different between groups.

(**Key words**: prepartum, propylene glycol, fatty liver, dairy cows)

Received March 25, 1993.
Accepted May 17, 1993.
[1]Reprint requests: 1675 Observatory Drive.

Abbreviation key: **PG** = propylene glycol, **RIA** = radioimmunoassay, **TG** = triglyceride.

INTRODUCTION

Fatty liver is a metabolic disorder associated with a decrease in animal production (10), reproductive performance (10), and immune competence (19). Decreased hepatic gluconeogenesis has also been associated with conditions conducive to fatty liver development (12). Recent evidence (31) suggests that fatty liver may precede clinical ketosis.

During periods of excessive fatty acid mobilization from adipose tissue, ruminants are prone to the development of fatty liver. Hepatic uptake of NEFA is positively related to plasma concentration (1). Once taken up by hepatocytes, fatty acids can either be completely oxidized to carbon dioxide, partially oxidized to acetyl-coenzyme A and released as ketone bodies or acetate, or esterified. Triglyceride (TG), the main esterification product, can be stored or exported within very low density lipoprotein. Accumulation of TG in isolated bovine hepatocytes increased as NEFA concentration increased in the media (5). Capacity for ruminants to export very low density lipoproteins is low (16, 23); thus, excessive TG accumulation is likely during rapid NEFA uptake by the liver.

Fatty liver is commonly considered to develop postpartum. However, hepatic TG accumulation is significant between 17 d prepartum and 1 d postpartum (2, 29). Estrogen, specifically estrone of placental origin, is elevated in late gestation and has been implicated in the development of fatty liver (13). Feed intake is depressed immediately prepartum (2), and negative energy balance and

NEFA release from adipose tissue can occur even prior to copious milk secretion. Recently, our laboratory (2) demonstrated that hepatic TG content at 1 d postpartum was significantly reduced in cows that were force-fed prepartum via rumen cannulas. Plasma glucose at 2 d prepartum also was elevated in force-fed cows and was negatively correlated with liver TG at d 1 postpartum.

Propylene glycol (PG) is a glucogenic compound used to treat ketosis postpartum. The majority of PG escapes the rumen intact; a portion is metabolized to propionate (7). Propylene glycol escaping rumen fermentation is converted to glucose by the liver, primarily via the lactaldehyde pathway and subsequent oxidation to lactate (18). Administration of PG to postpartum cows reduced plasma concentrations of NEFA and ketones (27). Addition of PG to the ration, compared with dietary starch, produced a greater molar percentage of rumen propionate and elicited a greater insulin response (9). The objective of our study was to determine whether prepartum administration of PG could reduce periparturient fatty liver.

MATERIALS AND METHODS

Experimental Design and Sampling Protocol

Twenty-four multiparous Holstein cows, pregnant and nonlactating, were initially paired according to calving date and assigned either to a control (n = 11) or PG treatment (n = 13) group. However, one cow assigned to the control group was mistakenly treated, leaving an unbalanced design. Cows began the trial at 21 d prior to expected calving and were fed alfalfa-bromegrass hay for ad libitum intake and 1.8 kg/d of concentrate separately to meet NRC (20) dry cow requirements. The prepartum concentrate contained 34% soybean meal, 18.3% cracked corn, 18.3% soybean hulls, 8.7% corn gluten meal, 8.7% blood meal, 8.7% meat and bone meal, 1.8% trace-mineralized salt, 1.3% vitamins A, D, and E (2,643,171 IU/kg of vitamin A, 881,057 IU/kg of vitamin D, and 881 IU/kg of vitamin E), and .3% magnesium oxide (DM basis). Following calving, cows were fed 50% alfalfa silage and 50% concentrate (DM basis) as a TMR for ad libitum intake. The postpartum concentrate contained 77.4% shell corn, 7.0% molasses, 6.0% liquid protein supplement, 4.7% soybean meal, 2.3% tallow, 1.6% sodium phosphate, .5% magnesium oxide, and .5% urea (DM basis). Feed and orts from each cow were sampled three times weekly. Three weekly samples were composited into one sample for each week. Forage and concentrate DM were determined by oven-drying at 60°C for calculation of DMI. Cows received a 1-L oral drench of PG (Phoenix Pharmaceutical, Inc., St. Joseph, MO) or water once daily at 1230 h from 7 d prior to expected calving until parturition.

Blood and plasma samples were as described by Skaar et al. (29) and were taken via the coccygeal vein on d 16 and 17 prior to expected calving. Blood was also sampled daily from 7 d prepartum to 3 d postpartum and on d 7, 14, and 21 postpartum. During treatment, blood samples were taken 90 min postdrenching. On d 5 prior to expected calving, additional blood was sampled at 15-min intervals postdrenching for 2.5 h. One cow assigned to the control group calved before multiple sampling. Liver was sampled by puncture biopsy at 17 d prior to expected calving and at 1 and 21 d postpartum. All plasma samples were analyzed in random order. Plasma was analyzed for glucose and NEFA (29). Plasma was deproteinized (29) following storage at –20°C and then immediately analyzed for BHBA (11). Plasma insulin was analyzed by radioimmunoassay (RIA) with a modification to the kit procedure (Coat-a-Count®; Diagnostic Products Co., Los Angeles, CA) to account for relatively low insulin concentrations in bovine plasma. Zero calibrator (100 μl) was added to 200 μl of each standard; the standard concentration was diluted by a factor of .66. Plasma (300 μl) was then used in the determination of each unknown sample. Insulin RIA intraassay variation was 7.9%, and interassay variation was 6.8%. Glucagon was analyzed by RIA according to the method of Reynolds et al. (25), except that Unger 30 K antibody was used. Glucagon RIA intraassay variation was 8.2%, and interassay variation was 6.0%. Liver tissue was assayed for total lipid and TG (29).

Milk production was recorded daily through 21 d postpartum. Milk samples were taken at a.m. and p.m. milkings on d 13, 14, 20, and 21 postpartum and analyzed for fat and protein percentages and somatic cells by infrared spectrophotometry (Wisconsin DHI Cooperative

Laboratory, Appleton, WI). Body weight and body condition score (6), averaged from two evaluators, were recorded once prior to treatment.

Statistical Analysis

Total liver lipid and TG were analyzed independently within sample period, i.e., 1 or 21 d postpartum, according to the following model: $Y_i = \mu + b + T_i + e_i$ where Y_i = the dependent variable, μ = the overall mean of the population, b = the regression coefficient for the liver variable measured at d 17 prior to expected calving, T_i = the average effect of treatment i, and e_i = the unexplained residual element assumed to be independent and normally distributed.

The DMI, analyzed independently within sample period (i.e., pre- or postpartum), milk production, and milk composition were analyzed according to the following model: $Y_{ijk} = \mu + T_i + C_j + P_k + TP_{ik} + e_{ijk}$ where Y_{ijk} = the dependent variable, μ = the overall mean of the population, T_i = the average effect of treatment i, C_j = the average effect of cow j, P_k = the average effect of period k, and e_{ijk} = the unexplained residual element assumed to be independent and normally distributed. Analysis of covariance using first lactation 305-d mature equivalent milk production as the regression coefficient was not successful in demonstrating differences in milk production. The regression coefficient was not included in the final statistical model for milk production. Period represented day for DMI and milk production and week for milk composition and FCM.

Plasma metabolites and hormones were analyzed independently within sample period (i.e., pre- or postpartum) according to the following model: $Y_{ijk} = \mu + b + T_i + C_j + P_k + TP_{ik} + e_{ijk}$ where Y_{ijk} = the dependent variable, μ = the overall mean of the population, b = the regression coefficient for the plasma variable averaged between measurements on d 16 and 17 prior to expected calving for cow j, T_i = the average effect of treatment i, C_j = the average effect of cow j, P_k = the average effect of period k, and e_{ijk} = the unexplained residual element assumed to be independent and normally distributed. Period represented day for daily plasma measurements and 15-min interval for multiple plasma samples. Models were originally constructed to contain pair (i.e., block), but the term was dropped because of events resulting in an uneven experimental design. Variation between cows was used as the error term when treatment effects on DMI, milk production and composition, and all plasma and liver measurements were tested. Differences were significant at $P < .05$, indicated a tendency at $P = .05$ to .15, and were nonsignificant at $P > .15$.

RESULTS AND DISCUSSION

Average BW and body condition score, measured prior to treatment, were not different between treatment groups (Table 1). Cows in

TABLE 1. Description of experimental cows.

	Control[1]		PG		P
	$\bar{X}$	SD	$\bar{X}$	SD	
BW (pretreatment), kg	712	83	699	64	.69
Body condition[2] (pretreatment)	3.2	.6	3.1	.5	.68
Parity	4.1	1.3	3.8	.8	.47
First lactation performance					
305-d Milk, kg	8045	745	7349	917	.05
305-d 3.5% FCM, kg	8230	819	7724	915	.17
305-d ME Milk,[3] kg	10,086	922	9663	1186	.35
Fat, %	3.6	.2	3.8	.3	.02
Protein, %	3.1	.1	3.2	.1	.32

[1]One liter of water (control) or propylene glycol (PG) given once daily as an oral drench beginning at an average of 8 d (control) or 10 d (PG) prepartum through parturition.

[2]Scale ranged from 1 = thin to 5 = obese.

[3]Mature equivalent.

the control group produced significantly more 305-d milk, and cows treated with PG had a greater fat percentage in their first lactation (Table 1), but 305-d 3.5% FCM and mature equivalent milk production were not different between groups. Treatment duration was 8 ± 2.5 d ($\bar{X}$ ± SD; range = 2 to 11 d) for the control group and 10 ± 3.6 d (range = 5 to 15 d) for the PG group. Multiple blood samples were obtained on d 6 ± 1.5 (range = 3 to 8) prepartum for the control group and d 7 ± 3.8 (range = 1 to 12) prepartum for the PG group.

Fisher et al. (8) reported a depression in forage DMI when PG was fed at 9% of the concentrate mixture (460 ml/d). However, to minimize the potential for confounding effects of PG and DMI, we delivered PG as an oral drench. Both groups experienced a moderate depression in feed intake immediately prepartum, but the depression was similar between treatments (Figure 1).

Plasma glucose was elevated by PG throughout treatment (Figure 2). Plasma glucose concentrations peaked at 75 min postdrenching (Figure 3). The elevation of plasma glucose agrees with that of other reports (9, 27), indicating that PG is an effective glucogenic agent. Plasma glucose increased dramatically in both groups at parturition (Figure 2), which agrees with results of Schwalm and Schultz (28). Increased plasma glucose concentration could be a result of increased gluconeogenesis, glycogenolysis, or both, stimulated by catecholamines and glucocorticoids (21) at parturition.

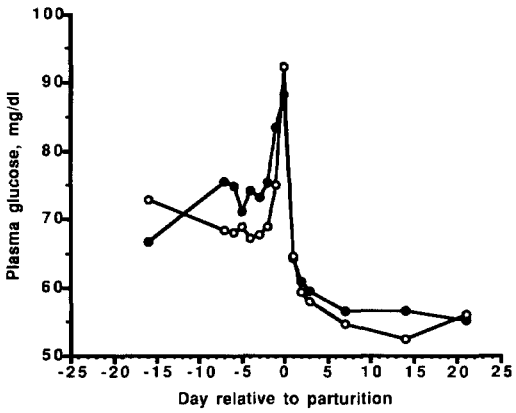

Figure 2. Plasma glucose concentration of cows given a drench of 1 L of water (○) or propylene glycol (●) once daily beginning at an average of 8 ± 2.5 d ($\bar{X}$ ± SD; range, 2 to 11 d) prepartum for cows assigned to the control group and 10 ± 3.6 d (range, 5 to 15 d) prepartum for cows treated with propylene glycol through parturition (unadjusted means). A prepartum treatment effect ($P < .01$) occurred. Postpartum plasma glucose concentrations were not significantly different between groups. The pre- and postpartum standard errors were 2.1 and 1.9 mg/dl, respectively.

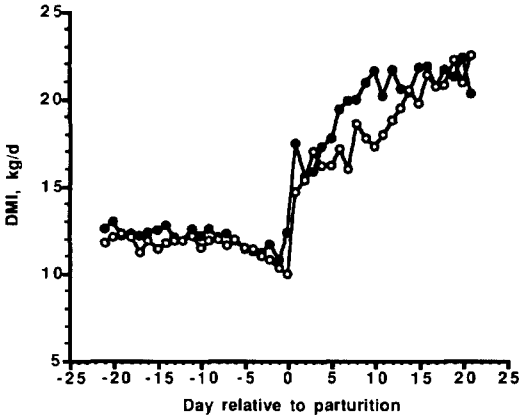

Figure 1. The DMI of cows given a drench of 1 L of water (○) or propylene glycol (●) once daily beginning at an average of 8 ± 2.5 d ($\bar{X}$ ± SD; range, 2 to 11 d) prepartum for cows assigned to the control group and 10 ± 3.6 d (range, 5 to 15 d) prepartum for cows treated with propylene glycol through parturition (unadjusted means). Differences in DMI were not significant between groups pre- or postpartum. The pre- and postpartum standard errors were .5 and .9 kg/d, respectively.

Plasma insulin concentrations were significantly elevated by 15 min following PG administration (Figure 4). Insulin concentration peaked prior to peak glucose concentration. Significant amounts of PG may have been metabolized to propionate, which stimulates pancreatic insulin secretion (14), or PG or intermediates of PG metabolism might be direct insulin secretagogues. Insulin concentrations were depressed on the day of calving (Figure 5), in contrast to results of Kunz et al. (17), who reported an insulin surge at calving. Our blood samples were taken at 24-h intervals; therefore, an acute insulin increase might not have been detected. Plasma insulin concentrations were not different between treatment groups following parturition.

Prepartum plasma glucagon concentration was not affected by prepartum PG administration (Figure 6), but daily samples were ob-

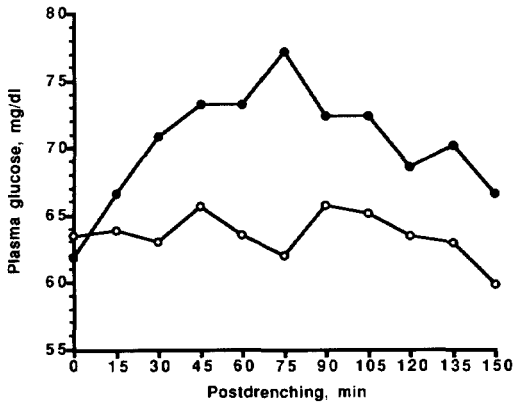

Figure 3. Plasma glucose concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) on d 6 ± 1.5 ($\bar{X}$ ± SD; range, 3 to 8) prepartum for cows assigned to the control group and d 7 ± 3.8 (range, 1 to 12) prepartum for cows treated with propylene glycol (unadjusted means). A treatment effect ($P < .01$) and a treatment by time interaction ($P < .05$) occurred. The overall standard error was 1.2 mg/dl.

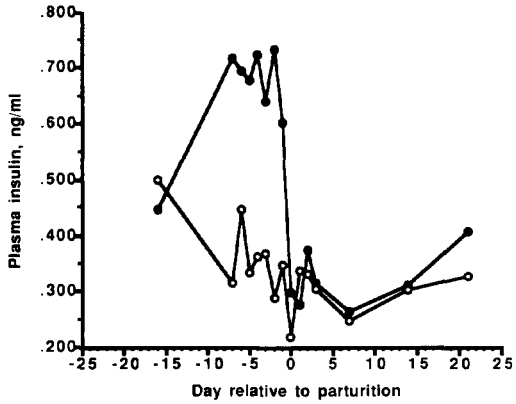

Figure 5. Plasma insulin concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) once daily beginning at an average of 8 ± 2.5 d ($\bar{X}$ ± SD; range, 2 to 11 d) prepartum for cows assigned to the control group and 10 ± 3.6 d (range, 5 to 15 d) prepartum for cows treated with propylene glycol through parturition(unadjusted means). A prepartum treatment effect ($P < .001$) occurred. Postpartum plasma insulin concentrations were not significantly different between groups. The pre- and postpartum standard errors were .034 and .030 ng/ml, respectively.

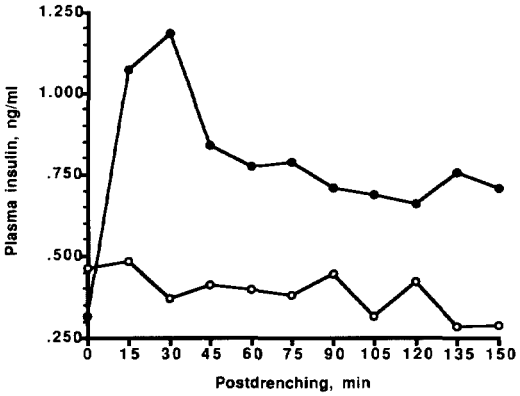

Figure 4. Plasma insulin concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) on d 6 ± 1.5 ($\bar{X}$ ± SD; range, 3 to 8) prepartum for cows assigned to the control group and d 7 ± 3.8 (range, 1 to 12) prepartum for cows treated with propylene glycol (unadjusted means). A treatment effect ($P < .001$) and a treatment by time interaction ($P < .001$) occurred. The overall standard error was .047 ng/ml.

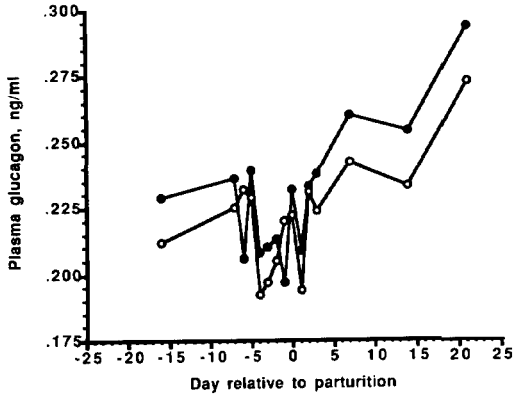

Figure 6. Plasma glucagon concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) once daily beginning at an average of 8 ± 2.5 d ($\bar{X}$ ± SD; range, 2 to 11 d) prepartum for cows assigned to the control group and 10 ± 3.6 d (range, 5 to 15 d) prepartum for cows treated with propylene glycol through parturition (unadjusted means). Pre- and postpartum plasma glucagon concentrations were not significantly different between groups. A day effect occurred across pre- and postpartum periods ($P < .001$). The pre- and postpartum standard errors were .006 and .009 ng/ml, respectively.

tained at 24-h intervals, and acute changes in plasma glucagon might not have been detected. However, differences between groups in plasma glucagon concentration were not detected in the prepartum multiple sample period (Figure 7). Plasma glucagon concentrations (Figure 6) were elevated as milk production and DMI increased, and a significant day effect existed across pre- and postpartum periods. Increasing blood VFA concentrations act directly on the pancreas to stimulate glucagon secretion in ruminants (14). Glucagon concentrations increase postpartum, which accompanies decreased plasma glucose and insulin. Glucose inhibits glucagon secretion (22).

Plasma NEFA concentration elevated gradually between d 16 and 2 prepartum in cows in the control group, but not in cows treated with PG (Figure 8). As previously noted by Reid et al. (24), the increase in plasma NEFA was sharp at calving. The increase in NEFA concentration between d 16 and 2 prepartum may be attributed to an increase in fetal glucose demand, followed by subsequent maternal reliance on fatty acids (30), depression in feed intake, possible catacholamine-stimulated lipolysis associated with stress at calving, or a combination of these factors. The relative contribution of the

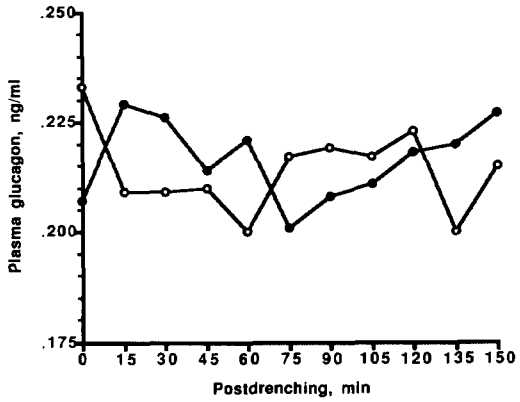

Figure 7. Plasma glucagon concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) on d 6 ± 1.5 ($\bar{X}$ ± SD; range, 3 to 8) prepartum for cows assigned to the control group and d 7 ± 3.8 (range, 1 to 12) prepartum for cows treated with propylene glycol (unadjusted means). Plasma glucagon concentrations were not significantly different between groups. The overall standard error was .009 ng/ml.

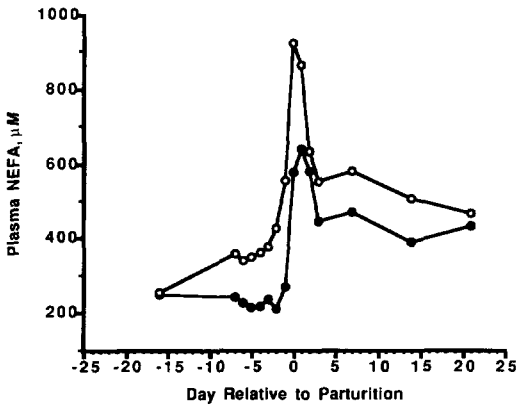

Figure 8. Plasma NEFA concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) once daily beginning at an average of 8 ± 2.5 d ($\bar{X}$ ± SD; range, 2 to 11 d) prepartum for cows assigned to the control group and 10 ± 3.6 d (range, 5 to 15 d) prepartum for cows treated with propylene glycol through parturition (unadjusted means). A prepartum treatment effect ($P < .001$), a postpartum treatment effect ($P < .10$), and a postpartum treatment by time interaction ($P < .10$) occurred. The pre- and postpartum standard errors were 28.8 and 52.7 μM, respectively.

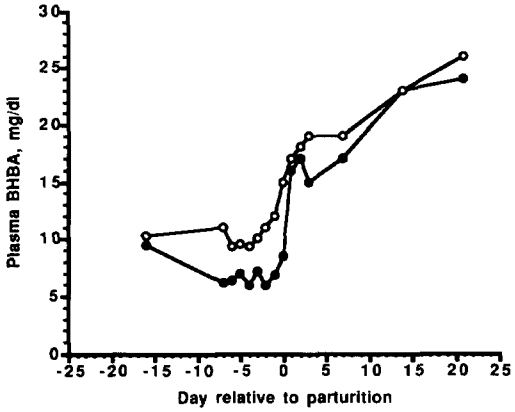

Figure 9. Plasma BHBA concentration of cows given a drench of 1 L of water (O) or propylene glycol (●) once daily beginning at an average of 8 ± 2.5 d ($\bar{X}$ ± SD; range, 2 to 11 d) prepartum for cows assigned to the control group and 10 ± 3.6 d (range, 5 to 15 d) prepartum for cows treated with propylene glycol through parturition (unadjusted means). A prepartum treatment effect ($P < .001$) occurred. Postpartum plasma BHBA concentrations were not significantly different between groups. The pre- and postpartum standard errors were .7 and 2.1 mg/dl, respectively.

TABLE 2. Effect of prepartum propylene glycol (PG) administration on total liver lipid and liver triglyceride (TG) concentration (DM basis).[1]

	Control[2]	SE	PG[2]	SE	*P*
Total liver lipid, %					
Day relative to parturition					
−16 (covariate period)	15.9	.4			
+01	29.5	2.3	21.1	2.1	.01
+21	31.4	2.8	22.3	2.1	.01
Liver TG, %					
−16 (covariate period)	1.6	.2			
+01	14.5	2.5	5.0	2.3	.01
+21	17.3	2.2	7.2	2.1	.01

[1]Data for d −16 are pooled and were used for analysis of covariance, and data for d 1 and 21 are covariately adjusted means.

[2]One liter of water (control) or PG given once daily as an oral drench beginning at an average of 8 d (control) or 10 d (PG) prepartum through parturition.

gradual increase in plasma NEFA concentration prior to parturition, or the acute surge at parturition, to development of hepatic TG accumulation is not known. Plasma NEFA concentration of cows treated with PG was significantly lower than that of cows in the control group prior to parturition, most likely because of inhibition of adipose adenylate cyclase activity and lipolysis by elevated plasma insulin (32). We have no explanation for the tendency toward lower postpartum plasma NEFA concentration in cows receiving PG because treatments were terminated at calving.

Prepartum plasma BHBA concentrations were decreased by PG treatment (Figure 9). Lower BHBA concentrations may reflect higher concentrations of insulin and lower concentrations of NEFA. Insulin may act to reduce NEFA supply to the liver, to inhibit hepatic ketogenesis, to increase ketone utilization by peripheral tissue (4), or trigger a combination of these effects. Postpartum plasma BHBA concentrations were similar between treatments.

At 1 d postpartum, total liver lipid and TG were significantly lower in cows treated with PG, and the differences were maintained through 21 d postpartum (Table 2). The difference in liver TG content postpartum accompanied a difference in plasma NEFA concentration between treatment groups. Changes in liver TG are a more sensitive measure of hepatic lipid accretion because they ignore phospholipid and cholesterol, which do not change markedly during elevated NEFA uptake (3). Both groups experienced a smaller increase in liver TG concentration between 1 and 21 d postpartum, which supports the concept that the majority of hepatic TG deposition occurs between 16 d prepartum and 1 d postpartum (12).

Correlation analysis was performed to identify prepartum parameters related to periparturient hepatic TG accumulation (Table 3). Prepartum plasma NEFA concentration was highly correlated with liver TG at 1 d postpartum. The likely importance of maintaining

TABLE 3. Correlation coefficients between prepartum plasma metabolites, hormones, DMI, or body condition score and liver triglyceride (TG) concentrations at 1 and 21 d postpartum.

	Liver TG			
Prepartum parameter[1]	1 d postpartum		21 d postpartum	
	r	*P*	r	*P*
Glucose	−.49	.02	−.36	.09
NEFA	.46	.03	.11	.60
BHBA	.36	.08	.45	.03
Insulin	−.49	.02	−.09	.69
Glucagon	.03	.91	−.07	.75
DMI	−.25	.24	−.22	.31
Body condition score[2]	.23	.29	.12	.56

[1]Plasma concentrations and DMI are expressed as means between d 1 and 7 prepartum.

[2]Scale ranged from 1 = thin to 5 = obese.

TABLE 4. Postpartum milk production, milk composition, and SCC.

	Control[1]	SE	PG[1]	SE	P
Milk production, kg/d	33.2	2.1	32.6	1.8	.75
3.5% FCM, kg/d	38.7	1.4	38.0	1.6	.69
Fat, %	3.97	.19	3.86	.11	.59
Fat, kg/d	1.42	.06	1.38	.06	.66
Protein, %	3.10	.10	3.11	.08	.86
Protein, kg/d	1.12	.03	1.11	.03	.95
SCC, 1000/ml	396	181	426	194	.90

[1]One liter of water (control) or propylene glycol (PG) given once daily as an oral drench beginning at an average of 8 d (control) or 10 d (PG) prepartum through parturition.

prepartum plasma glucose and insulin concentrations in indicated by their strong negative correlation with liver TG at 1 d postpartum, but not at 21 d postpartum. Plasma BHBA concentration and liver TG accumulation were positively correlated at 1 and 21 d postpartum.

Milk production and composition were not affected by prepartum PG administration (Table 4). In a previous study (2), cows force-fed via rumen cannulas had a lower liver TG content at 1 d postpartum and produced more milk through 28 d postpartum. Longer postpartum periods would be desirable for detection of treatment effects on milk production. Cows used in this experiment were in moderate body condition (Table 1). Production benefits from PG administration may have been realized if experimental cows had been in excessive body condition, possibly predisposing them to fatty liver and ketosis (24). Differences between groups in animal health were not observed.

The PG dose given in this study was in excess of the standard postpartum field recommendation of 230 to 410 ml/d (15). The minimum effective prepartum dose of PG for the alleviation of fatty liver is unknown. A summary of data from our laboratory and other reports (9, 26, 27) indicate that the antilipolytic effect of PG increases linearly from 117 ml/d of PG to 1 L/d of PG (r^2 = .86).

CONCLUSIONS

Prepartum PG administration reduced hepatic TG accumulation by 32 and 42% at 1 and 21 d postpartum, respectively. Evidence from this experiment suggests that reducing prepartum plasma NEFA concentration is important for reducing periparturient hepatic TG accumulation. This reduction could be achieved by improved energy balance in late gestation through maintenance of prepartum DMI, enhanced carbohydrate and insulin status through administration of glucogenic precursors during the last few days of gestation, or both. Increasing dietary nonstructural carbohydrates may have limited effectiveness, considering the inherent decline in feed intake immediately prepartum and complications that can arise from rumen acidosis. Administration of PG elevated prepartum plasma glucose concentrations; however, the stimulation of insulin secretion probably more directly modulated prepartum plasma NEFA concentration. Further research is needed to evaluate the possible role of insulin as a preventative agent in the alleviation of periparturient fatty liver.

ACKNOWLEDGMENTS

The care and feeding of the experimental cows was coordinated by Leland Danz, whose contribution is greatly appreciated. The authors also thank Dawn Miksic for her assistance in the laboratory.

REFERENCES

1 Bell, A. W. 1980. Lipid metabolism in the liver and selected tissues and in the whole body of ruminant animals. Prog. Lipid Res. 18:117.

2 Bertics, S. J., R. R. Grummer, C. Cadorniga-Valino, and E. E. Stoddard. 1992. Effect of prepartum dry matter intake on liver triglyceride concentration and early lactation. J. Dairy Sci. 75:1914.

3 Butler, S. M., A. Faulkner, V. A. Zammit, and R. G. Vernon. 1988. Fatty acid metabolism of the perfused caudate lobe from livers of fed and fasted nonpregnant and fasted late pregnant ewes. Comp. Biochem. Physiol. B. Comp. Biochem. 91:25.

4 Brockman, R. P. 1979. Roles of insulin and glucagon in the development of ruminant ketosis: a review. Can. Vet. J. 20:121.

5 Cadorniga, C. P., R. R. Grummer, L. E. Armentano, and S. S. Donkin. 1992. Effects of extracellular fatty acid concentration, estriol, insulin, and glucagon on hepatic triglyceride accumulation, acid soluble product formation, and gluconeogenesis. J. Dairy Sci. 75(Suppl. 1):183.(Abstr.)

6 Edmonson, A. J., I. J. Lean, L. D. Weaver, T. Farver, and G. Webster. 1989. A body condition scoring chart for Holstein dairy cows. J. Dairy Sci. 72:68.

7 Emery, R. S., N. Burg, L. D. Brown, and G. N. Blank. 1964. Detection, occurrence, and prophylactic treatment of borderline ketosis with propylene glycol feeding. J. Dairy Sci. 47:1074.

8 Fisher, L. J., J. D. Erfle, G. A. Lodge, and F. D. Sauer. 1973. Effects of propylene glycol or glycerol supplementation of the diet of dairy cows on feed intake, milk yield and composition, and incidence of ketosis. Can. J. Anim. Sci. 53:289.

9 Fronk, T. J. 1975. The effect of propylene glycol on milk fat depression. M.S. Thesis, Univ. Wisconsin, Madison.

10 Gerloff, B. J., T. H. Herdt, and R. S. Emery. 1986. The relationship of hepatic lipidosis to health and performance in dairy cattle. J. Am. Vet. Med. Assoc. 188:845.

11 Gibbard, S., and P. J. Watkins. 1968. A micro-method for the enzymatic determination of d-β-hydroxybutyrate and acetoacetate. Clin. Chim. Acta 19:511.

12 Grummer, R. R. 1993. Etiology of lipid-related metabolic disorders in periparturient cattle. J. Dairy Sci. 76 (Nov).

13 Grummer, R. R., S. J. Bertics, D. W. LaCount, J.A. Snow, M. R. Dentine, and R. H. Stauffacher. 1990. Estrogen induction of fatty liver in dairy cattle. J. Dairy Sci. 73:1537.

14 Harmon, D. L. 1992. Impact of nutrition on pancreatic exocrine and endocrine secretion in ruminants: a review. J. Anim. Sci. 70:1290.

15 Herdt, T. H., and R. S. Emery. 1992. Therapy of diseases of ruminant intermediary metabolism. Vet. Clin. North Am. Food Anim. Pract. 8:91.

16 Kleppe, B. B., R. J. Aiello, R. R. Grummer, and L. E. Armentano. 1988. Triglyceride accumulation and very low density lipoprotein secretion by rat and goat hepatocytes in vitro. J. Dairy Sci. 71:1813.

17 Kunz, P. L., J. W. Blum, I. C. Hart, H. Bickel, and J. Landis. 1985. Effects of different energy intakes before and after calving on food intake, performance and blood hormones and metabolites in dairy cows. Anim. Prod. 40:219.

18 Miller, O. N., and G. Bazzano. 1965. Propanediol metabolism and its relation to lactic acid metabolism. Ann. New York Acad. Sci. 119:957.

19 Morrow, D. A., D. Hillman, A. W. Dade, and H. Kitchen. 1979. Clinical investigation of a dairy herd with the fat cow syndrome. J. Am. Vet. Med. Assoc. 174:161.

20 National Research Council. 1989. Nutrient Requirements of Dairy Cattle. 6th rev. ed. Natl. Acad. Sci., Washington, DC.

21 Norman, A. W., and G. Litwack. 1987. Adrenal corticoids. Page 412 *in* Hormones. Academic Press, San Diego, CA.

22 Pipeleers, D. G., F. C. Schuit, C. Van Schravendijk, and M. Van De Winkel. 1985. Interplay of nutrients and hormones in the control of glucagon release. Endocrinology 117:817.

23 Reid, I. M, R. A. Collins, G. D. Baird, C. J. Roberts, and H. W. Symonds. 1979. Lipid production rates and the pathogenesis of fatty liver in fasted cows. J. Agric. Sci. (Camb.) 93:253.

24 Reid, I. M., C. J. Roberts, R. J. Treacher, and L. A. Williams. 1986. Effect of body condition at calving on tissue mobilization, development of fatty liver and blood chemistry of dairy cows. Anim. Prod. 43:7.

25 Reynolds, C. K., H. F. Tyrell, and L. E. Armentano. 1992. Effects of mesenteric vein *n*-butyrate infusion on liver metabolism by beef steers. J. Anim. Sci. 70: 2250.

26 Ruegsegger, G. J., and L. H. Schultz. 1986. Use of a combination of propylene glycol and niacin for subclinical ketosis. J. Dairy Sci. 69:1411.

27 Sauer, F. D., J. D. Erfle, and L. J. Fisher. 1973. Propylene glycol and glycerol as a feed additive for lactating dairy cows: an evaluation of blood metabolite parameters. Can. J. Anim. Sci. 53:265.

28 Schwalm, J. W., and L. H. Schultz. 1976. Relationship of insulin concentration to blood metabolites in the dairy cow. J. Dairy Sci. 59:255.

29 Skaar, T. C., R. R. Grummer, M. R. Dentine, and R. H. Stauffacher. 1989. Seasonal effects of prepartum and postpartum fat and niacin feeding on lactation performance and lipid metabolism. J. Dairy Sci. 72: 2028.

30 Speroff, L. 1981. The ovary. Page 684 *in* Endocrinology and Metabolism. P. Felig, J. D. Baxter, A. E. Broadus, and L. A. Frohman, ed. McGraw-Hill, New York, NY.

31 Veenhuizen, J. J., J. K. Drackley, M. J. Richard, T. P. Sanderson, L. D. Miller, and J. W. Young. 1991. Metabolic changes in blood and liver during development and the treatment of experimental fatty liver and ketosis in cows. J. Dairy Sci. 74:4238.

32 Vernon, R. G. 1980. Lipid metabolism in the adipose tissue of ruminant animals. Prog. Lipid Res. 19:23.