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Short Communication
Preventative Effect of Oral Administration of Propylene Glycol and Bypass Amino Acids on the Development of Ketosis in Dairy Cows

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Abstract

Background and Objectives: Ketosis in dairy cow after parturition is a disease in dairy farms chiefly caused by lack of energy. It was examined that the preventative effect of oral administration of propylene glycol and feeding bypass amino acids prospectively on ketosis in dairy cows. **Materials and Methods:** Sixteen Holstein cows, serum total cholesterol concentrations <87 mg dL^{-1} (72±10 mg dL^{-1}) at 2 weeks before parturition that were at risk of developing ketosis after parturition, were randomly assigned to 3 groups. Seven cows were not treated (NT group), 5 cows were orally treated with 90% propylene glycol upto parturition at 250 mL/day/head for 10 days (PPG group) and 4 cows were given a combined treatment of propylene glycol in the same way as the PPG group and were also fed bypass amino acids at 400 g/day/head from -7-14 of parturition for 21 days (PPG+BAA group). The results of 3 groups for incidence of ketosis, treatment days, blood examination (serum 3-Methylhistidine, NEFA, TCho, BUN, Alb, AST, GGT) and BCS were compared. Numbers of cows with ketosis were analyzed by chi-square test. **Results:** The incidence of ketosis in the NT group was higher than in the PPG+BAA group significantly ($p<0.05$). The serum 3-Methylhistidine concentration in the NT group was higher than in the PPG+BAA group at 2 weeks after parturition ($p<0.05$). The serum GGT activity in the NT group was higher than the normal range at 0, 2 and 4 weeks of parturition and was significantly higher than those in the other two groups at 2 weeks after parturition ($p<0.05$). **Conclusion:** These findings suggested that administration of propylene glycol and feeding bypass amino acids controls the acceleration of body protein degradation and prevents liver dysfunction. This is an effective method for prevention of ketosis in dairy cows.

Key words: Body protein degradation, gluconeogenesis, ketosis, periparturient, propylene glycol, 3-Methylhistidine

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ketosis in dairy cows occurs chiefly due to a lack of energy during the periparturient period[1-10]. Lack of energy in dairy cows is associated with an acceleration in gluconeogenesis from amino acids and consequently a reduction in their levels[2,11]. Just after parturition, milk protein production increases rapidly, reducing amino acid levels even further. When amino acids are lacking, body proteins are degraded into amino acids. Tri-methylhistidine is an amino acid produced by protein degradation in skeletal muscle[2,11,12]. However, unlike other amino acids, it is often unused and enters the circulation. Therefore, the serum 3-Methylhistidine concentration is a sensitive index of protein degradation and serves as a marker of the lack of protein[2,11,12]. Serum 3-Methylhistidine concentrations in cows with ketosis are higher than those of healthy cows after parturition[2]. These findings suggest that cows with ketosis are lacking both energy and amino acids. Usual method to prevent ketosis is administration of energy source material such as propylene glycol, which is metabolized in the liver by alcohol dehydrogenase to lactic acid and then puruvic acid[4,5]. Therefore, the preventative effect of oral administration of propylene glycol was examined in this study and feeding bypass amino acids on the development of ketosis in dairy cows was also investigated.

MATERIALS AND METHODS

This study was carried out in Shizuoka Prefectural Animal Industry Research Institute.

Animals: About 16 Holstein cows with serum total cholesterol concentrations <87 mg dL^{-1} (72±10 mg dL^{-1}) at 2 weeks before parturition, which were at risk of developing ketosis after parturition were selected for this study. Cows were 3-8 years old. Twelve cows calved between November, 2002 and January, 2005 and 4 cows calved between September, 2014 and August, 2016. The cows were raised at the Shizuoka Prefectural Livestock Experiment Station and were individually kept in tie stalls from -21-30 days of parturition. They were then kept in a free stall barn from 31 days after parturition. They were fed orchard grass silage, oat and timothy hays and a mixed concentrate (TDN/DM 78.0% and CP/DM 17.0%) during the late dry period. The quantity of mixed concentrate was increased gradually. The average nutrient composition of the dairy ration during the dry period was as follows: 67.6% for TDN/DM, 11.4% for CP/DM, 69.8% for DCP/CP, 26.7% for CF/DM, 29.2% for ADF, 46.2% for NDF and 1.25% for DM/BW, respectively. Cows received a total mixed ration consisting of orchard grass silage, oat, timothy and alfalfa hays, soybean meal, rolled maize grain, rolled barley, mineral and vitamin supplements and a mixed concentrate (TDN/DM 78.0% and CP/DM 17.0%) during the early lactation period. The average nutrient composition was as follows: 75.2% for TDN/DM, 16.7% for CP/DM, 62.3% for DCP/CP, 20.3% for CF/DM, 23.7% for ADF, 38.9% for NDF and 4.36% for DM/BW, respectively.

Experimental groups: A control group of 7 cows was not given any treatment (NT group). Four cows in this group had been used in an experiment reported previously[2]. Their serum total cholesterol (TCho) concentrations were <87 mg dL^{-1} at 2 weeks before parturition, which meant that they were suitable for inclusion in the NT group for this study. Four cows were given 90% propylene glycol (Neorunogen, Kyoritsu-seiyaku, Tokyo, Japan) orally at 250 mL/day/head from -14-0 days of parturition (PPG group). Four cows were treated in the same way as the PPG group and were also fed bypass amino acids (Zenrakuren, Tokyo, Japan) at 400 g/day/head from -7-14 days of parturition (PPG+BAA group). The components of the bypass amino acids (% for CP) were as follows: Methionine 1.55%, Lysine 6.24%, Arginine 7.74%, Threonine 4.18%, Leucine 8.31%, Isoleucine 5.09%, Valine 5.43%, Histidine 2.82%, Phenylalanine 5.54% and Tryptophan 1.27%.

Diagnosis and treatment of ketosis: The cows were observed daily for signs of ketosis. The criteria for ketosis were poor appetite and vitality and a β-hydroxybutyrate concentration of >200 μmol L^{-1} in their milk (San Keto Paper, Sanwa Kagaku Kenkyusho, Nagoya, Japan). All cows with a diagnosis of ketosis were treated with intravenous infusions of 25% (w/v) xylitol solution.

Blood test and body condition score: Blood samples were collected in the morning before feeding at 2 weeks before parturition (-13±6 days of parturition), 0 week (day of parturition), 2 weeks after parturition (16±2 days of parturition) and 4 weeks after parturition (29±2 days of parturition). Blood was collected within 24 h of calving. The serum 3-Methylhistidine concentration was determined by high performance liquid chromatography after converting the fluorescamine derivatives by treatment with perchloric acid (Wako pure chemical industries, Osaka, Japan) and heating at 80°C for 1 h[13]. The blood urea nitrogen (BUN), serum albumin (Alb), TCho concentrations, aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase

(GGT) activities were determined by the dry-chemistry method (Dri-Chem 3000V, Fujifilm Technomedical, Tokyo, Japan) and the NEFA concentration was determined using an automatic analyzer (JCA-BM2250, Nippon Denshi Kogyo, Tokyo, Japan). Body condition score (BCS) on a scale of 1-5 with 0.25 intervals was estimated at the time of blood sampling[14].

This study was conducted in a manner consistent with the guidelines for animal experimentation of the Shizuoka Prefectural Animal Industry Research Institute.

Statistical analysis: Numbers of cows with ketosis in the 3 groups were analyzed by chi-square test and $p<0.05$ was considered to be significant. The other data from the three groups were expressed as means±standard deviation and analyzed using Steel test and $p<0.05$ was considered to be significant.

RESULTS

The numbers of ketotic cows and their treatment days are shown in Table 1. Five cows developed ketosis in the NT group and their treatment days were 3.4±3.8. Three cows developed ketosis in the PPG group and their treatment days were 1.4±1.3. None of the cows in the PPG+BAA group developed ketosis and their treatment days were 0. The number of ketotic cows in the NT and PPG+BAA groups were significantly different ($p<0.05$). The treatment days of PPG+BAA group showed less tendency, but were not significantly different compared with other 2 groups.

The results of blood tests and body condition scores are shown in Table 2. The serum 3-Methylhistidine concentrations of 3 cows in NT group and a cow in PPG group were missing data. The serum 3-Methylhistidine concentration in the NT group was higher than in the PPG+BAA group at 0 and 2 weeks after parturition ($p<0.05$). The serum NEFA concentration in the NT group was higher than the normal

Table 1: Numbers of cows with ketosis and their treatment days in the 3 groups

Groups	Numbers of cows with ketosis/experimental cow	Treatment days of ketosis
NT	5/7*	3.4±3.8
PPG	3/5	1.4±1.3
PPG+BAA	0/4*	0

Numbers of cows with ketosis are indicated for each group and were examined by chi-square test. *: Asterisks indicate significant differences of $p<0.05$. Values of treatment days are expressed as Means±SD. Differences in mean values between the 3 groups were examined by Steel test

Table 2: Serum 3-Methylhistidine, lipid and protein concentrations, enzyme activities and body condition scores of the 3 groups

			Weeks from parturition			
Variables	Groups	n	-2w	Ow	2w	4w
3-Methylhistidine (nmol mL^{-1})	NT	4	15.0±6.3	23.1±7.8	12.6±2.5	6.8±1.8
	PPG	4	8.1±5.1	17.7±14.1	11.5±4.9	5.6±1.4
	PPG+BAA	4	10.4±1.5	11.4±2.2*	6.1±2.0*	5.3±1.2
NEFA (μEqL^{-1})	NT	7	226±124	920±754	463±131	593±468
	PPG	5	153±61	761±485	492±211	283±142
	PPG+BAA	4	159±60	573±397	291±206	334±283
TCho (mg dL^{-1})	NT	7	67±13	69±14	111±28	174±48
	PPG	5	77±5	60±10	126±25	168±23
	PPG+BAA	4	73±8	60±11	127±28	173±17
BUN (mg dL^{-1})	NT	7	7.6±2.1	10.1±3.0	8.6±2.2	10.7±2.8
	PPG	5	8.8±2.7	10.6±4.0	11.9±2.6	12.6±2.2
	PPG+BAA	4	9.0±3.3	8.5±1.2	12.0±1.5	14.4±2.5
Alb (mg dL^{-1})	NT	7	3.2±0.4	3.4±0.3	3.3±0.4	3.5±0.4
	PPG	5	3.4±0.2	3.4±0.2	3.7±0.4	3.6±0.2
	PPG+BAA	4	3.4±0.2	3.5±0.3	3.6±0.3	3.8±0.2
AST (IU L^{-1})	NT	7	62±25	67±13	127±46	108±31
	PPG	5	48±8	65±10	74±11	71±10
	PPG+BAA	4	72±47	83±55	111±76	87±31
GGT (IU L^{-1})	NT	7	17.1±5.9	24.4±8.8	27.9±8.2	30.7±9.4
	PPG	5	15.6±6.0	19.1±9.3	16.8±5.7*	20.4±7.5
	PPG+BAA	4	9.3±3.0	15.7±15.5	12.0±1.5*	17.8±5.1
BCS	NT	7	3.29±0.33	3.04±0.27	3.05±0.33	2.75±0.43
	PPG	5	3.19±0.43	3.00±0.56	2.85±0.38	2.88±0.43
	PPG+BAA	4	3.44±0.66	3.25±0.35	3.00±0.35	2.94±0.38

Values are expressed as Means±SD. Differences in mean values between the 3 groups sampled on the same day were examined by Steel test, *Asterisks indicate significant differences of $p<0.05$ compared with NT group, NEFA: Non-esterified fatty acid, TCho: Total cholesterol, BUN: Blood urea nitrogen, Alb: Albumin, AST: Aspartate aminotransferase, GGT: r-glutamyl transpeptidase, BCS: Body condition score

range but not significantly different from the other 2 groups. The serum TCho concentration of all experimental cows at 2 weeks before parturition was <87 mg dL^{-1} (72±10 mg dL^{-1}) which was below normal, although concentrations at 0, 2 and 4 weeks after parturition were almost within the normal range and not significantly different between the 3 groups. The serum GGT activity in the NT group was higher than the normal range at 0, 2 and 4 weeks after parturition and was significantly different from the PPG and PPG+BAA groups at 2 weeks after parturition ($p<0.05$). The other variables (BUN, Alb, AST and BCS) were not significantly different between the 3 groups.

DISCUSSION

The stage at which cholesterol metabolism is no longer sufficient for maintaining TCho concentrations at normal levels occurs before parturition in cows with ketosis. These findings suggested that oral administration of 90% propylene glycol at 250 mL/day/head for 10 days is not sufficient to completely prevent ketosis. However, the combined administration of propylene glycol and bypass amino acids was effective in preventing the development of ketosis.

Serum 3-Methylhistidine is a sensitive index of protein degradation in skeletal muscle[2,11,12]. In this study, the serum 3-Methylhistidine concentration of the NT group was significantly higher than that of the PPG+BAA group at 0 and 2 weeks after parturition. This suggests that the combination of propylene glycol and bypass amino acids treatment can control the acceleration of body protein degradation. The serum NEFA concentration is an index of body fat degradation and tends to increase in cows with ketosis[1-3,5,6,15]. The serum NEFA concentration of the NT group was higher than the normal range on parturition day but not significantly different from the PPG and PPG+BAA groups. This suggests that the treatment with 90% propylene glycol is not enough to control the acceleration of body fat degradation. If the cows were treated with propylene glycol at >250 mL/day/head, the acceleration of body fat degradation might be controlled. However, it has been reported that a large quantity of propylene glycol produces sulfur containing gases in the rumen and may contribute to toxic effects[7]. This study suggests that the administration of propylene glycol and bypass amino acids in combination reduces the amount of propylene glycol required and prevents ketosis without causing disorders in ruminal fermentation. The serum TCho concentration is an index of energy metabolism and is influenced by energy intake from feed. The serum TCho concentration in cows with ketosis is lower compared with healthy cows before parturition[2,15] but following parturition the concentration in cows with ketosis is reduced for variable periods of time. Akamatsu *et al*.[2], reported that the serum TCho concentration in cows with ketosis was lower than that of healthy cows at 30 days after parturition. Shibano and Kawamura[15], reported that the serum TCho concentration in cows with hepatic lipidosis involving ketone body rise was lower than that of cows with non-hepatic lipidosis one day after parturition but was not different between the two groups at 7, 14, 30 and 60 days after parturition. It is suggested that these different findings are caused by variations in feeding management practices. It was found that serum TCho concentrations in the NT group after parturition were almost within the normal range and not different from the PPG and PPG+BAA groups. This suggests that the serum TCho concentration in cows with ketosis is not always lowered after parturition. The serum BUN and Alb concentrations were not significantly different between the 3 groups in this study, suggesting that while acceleration of protein degradation occurs, protein synthesis in the rumen and liver did not decrease in cows with ketosis. Serum AST activity is an index of internal injury in both liver and skeletal muscle. The serum AST activities were not significantly different between the three groups in this study. Serum GGT activity is an index of liver function related to bile excretion. The serum GGT activity in the NT group was higher than the normal range at 0, 2 and 4 weeks after parturition and significantly higher than that of the PPG and PPG+BAA groups at 2 weeks after parturition. This suggests that liver dysfunction related to an insufficiency of bile excretion occurs in cows with ketosis and the oral administration of propylene glycol prevents a decrease in liver function. The BCS were almost within the normal range and not significantly different between the three groups. This suggests that BCS is not always related to acceleration in body protein degradation or development of ketosis.

CONCLUSION

Authors have shown that the combined administration of propylene glycol and feeding bypass amino acids can control the acceleration of body protein degradation and prevent the liver dysfunction. It is proposed that its more effective method to prevent ketosis than the usual method to administer the energy supplement only.

SIGNIFICANCE STATEMENTS

This study discovers the possible synergistic effect of propylene glycol and feeding bypass amino acids that can be

beneficial for prevention of ketosis in dairy cows after parturition. This study will help the farmers and veterinarians to prevent ketosis after parturition and will be beneficial for future research on prevention of ketosis.

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