ABSTRACT

Intravenous administration of 500 ml of 50% glucose solution to 10 nonketotic dairy cows increased the blood glucose and insulin concentrations 7-fold immediately following administration. Blood glucose and insulin concentrations of ketotic cows were about 6- and 3-fold higher, respectively, immediately following glucose administration. Administration of 1000 ml of 25% xylitol (xylo-pentane-1,2,3,4,5-pentol) in nonketotic cows increased blood glucose and insulin concentrations 2- and 9-fold, respectively. Ketotic cows treated with xylitol exhibited blood insulin concentration 12-fold higher following administration. This insulin increase might be explained by a decrease in insulin degradation because of the diffusion of xylitol, which is not dependent on insulin in peripheral tissues. For ketotic cows given xylitol, serum concentrations of free fatty acid decreased, and triglyceride concentrations and aspartic acid aminotransferase activity increased, but values were unchanged by xylitol administration to nonketotic cows. Thus, for ketotic cows, the responses of the blood glucose and insulin concentrations to xylitol administration were better than those responses to glucose administration. Improvements in clinical signs, i.e., disappearance of urinary ketone bodies and recovery to normal feed consumption, also suggested the usefulness of xylitol administration for the treatment of ketosis.

(Key words: dairy cow, glucose, tolerance test, xylitol)

Abbreviation key: AST = aspartate acid aminotransferase, 11-OHCS = 11-hydroxycorticosterone.

INTRODUCTION

Ketosis is a condition that elevates the concentrations in bodily fluids of ketone bodies, such as acetoacetate, 3-hydroxybutyrate, and acetone. Ketosis, which is frequently encountered in dairy cows receiving a shortage of high quality, unprocessed grains, is caused by metabolic disturbances of carbohydrates and volatile fatty acids (12, 13). Dairy cows must produce large amounts of glucose by gluconeogenesis to meet the heavy demands for lactose, particularly during early lactation when the demand is the greatest. If cows cannot meet even a slight additional demand for glucose, they become glucose deficient and overproduce ketones; consequently, ketosis ensues (11). Endocrine disorders probably also contribute to the etiology of this disease (6, 9, 15). In ketotic cows, the blood insulin concentration is lower and the glucagon concentration is higher than concentrations in healthy cows before glucose administration. This increase might be due to reduced responsiveness of insulin secretion and to decreased B-cell function in the pancreas of a ketotic cow.

Glucose and organic acids have been used for the treatment of ketosis in dairy cows. Xylitol, which stimulates insulin secretion, has been used for treatment of human diabetes and has marked antiketotic action (8). However, few reports (5) exist on the treatment of ketotic cows with xylitol. In our study, nonketotic and ketotic cows were examined for glucose tolerance after intravenous injection of glucose or xylitol, and the physiological and therapeutic effects over time were compared.

MATERIALS AND METHODS

Cows

Twenty Holstein cows, 10 nonketotic and 10 ketotic, were used. Cows, 3 to 5 yr of age and within 1 mo of parturition, were located at private dairy farms in eastern Saitama Prefecture. Ketosis was described by clinical signs, such as loss of appetite, decreased milk production, and the presence of ketone bodies in urine. These signs were absent in the 10 cows assigned to the nonketotic group (Figure 1).

Administration of Glucose and Xylitol

Prior to administration of glucose or xylitol, the bladder of each cow was evacuated by urethral
GLUCOSE AND XYLITOL TOLERANCE OF COWS

373

using test tape (Labstix; Miles-Sankyo, Tokyo, Japan).

Statistical Analyses

Statistical analyses were performed using the linear models procedure of SAS (20), and separation of means was performed by preplanned single degree of freedom comparisons. Comparisons were considered to be significant at $P < 0.05$.

RESULTS

Blood Glucose and Insulin Concentrations of Nonketotic Cows

Immediately following glucose administration (Figure 2), the blood glucose concentration increased 6.4-fold ($320 \pm 11.9$ mg/dl; $\bar{X} \pm SE$) from $50.1 \pm 7.5$ mg/dl before administration ($P < 0.05$). Glucose concentrations decreased thereafter: $195 \pm 12$ mg/dl by 15 min, $160 \pm 12$ mg/dl by 30 min, $130 \pm 10$ mg/kg by 45 min, and $115 \pm 12$ mg/kg by 60 min. Concentrations at 2 h, $52 \pm 15$ mg/kg, were not different from baseline values. The regression equation for these

catheterization using a rubber urinary catheter (Fuji-hira Kogyo, Tokyo, Japan). One-half of each group was given a 500-ml volume of a 50% glucose solution (Zenyaku Kogyo, Tokyo, Japan) via intravenous drip over a 12- to 15-min period. The other half of each group received 1000 ml of 25% xylitol (Zenyaku Kogyo) in the same manner.

Sample Collection

Blood samples were collected from the jugular vein using vacutainer tubes 15 min (0.25 h) before; immediately after; and 15, 30, 45, 60, and 120 min after administration of the two solutions. Blood samples were obtained for serum. Samples were assayed for glucose by the enzymatic method of Sakai et al. (19), for xylitol by the method of Horn et al. (8), for insulin by radioimmunoassay (22), for free fatty acids by enzymatic method (14), for triglycerides by enzymatic method (16), for total cholesterol by enzymatic method (1), for aspartate acid aminotransferase (AST) by UV method (18), and for 11-hydroxycorticosterone (11-OHCS) by the method of De Moor et al. (4). Urinary ketones were measured

Figure 1. Comparison of milk production between nonketotic and ketogenic cows at d 13 to 15 postpartum. Vertical bars represent the standard error of mean. Asterisk indicates difference ($P < 0.05$) between groups.

Figure 2. Changes in the blood glucose of nonketotic and ketogenic cows after administration of glucose (●) and xylitol (○). Vertical bars represent the standard error of the mean. Asterisk indicates difference ($P < 0.05$) between groups.

Mean blood glucose then gradually decreased 240 ± 13 mg/dl by 15 min, 185 ± 2 mg/dl by 30 min, and 138 ± 9 mg/dl by 60 min. The regression equation for these changes was \( y = 301 - 62x \). For the group receiving xylitol, the blood glucose concentration showed little difference until 30 min (50 ± 10 mg/dl) after xylitol administration but increased 1.6 times after 60 min (62 ± 7 mg/dl) compared with the value before administration (39 ± 5 mg/dl) (Figure 2).

For the group that was administered glucose, the blood insulin concentration increased 4.6-fold immediately after administration (39.8 ± 6.5 μU/ml) compared with baseline concentrations (8.6 ± 0.9 μU/ml) (Figure 3). Blood insulin decreased gradually thereafter to 38.7 ± 7.0 μU/ml at 15 min, 30.4 ± 6.0 μU/ml at 30 min, 16.8 ± 2.0 μU/ml at 60 min, and nearly to the preadministration concentration, 9.3 ± 2.6 μU/ml, at 2 h. For the group receiving xylitol, the pattern for blood insulin change was different from that of the glucose group. Blood insulin increased 5.1-fold immediately after administration (44.0 ± 9.8 μU/ml) and increased more markedly to 12.8-fold after 15 min (109.8 ± 17.7 μU/ml) compared with baseline concentrations (\( P < 0.05 \)). Blood insulin decreased gradually from 90.6 ± 19.2 μU/ml at 30 min after

**Figure 3.** Changes in the blood insulin of nonketotic and ketotic cows after administration of glucose (●) and xylitol (○). Vertical bars represent the standard error of the mean. Asterisk indicates difference (\( P < 0.05 \)) between groups.

Changes was \( y = 318 - 43x \). The mean blood glucose concentrations following administration of xylitol were not different from baseline concentrations until 60 min after the administration (49 ± 10 mg/dl). Blood glucose was 1.9 times higher (97 ± 10 mg/dl) than baseline concentrations at 2 h (Figure 2).

Blood insulin concentration was 5.2 times higher (75.5 ± 7.6 μU/ml) immediately after the administration of glucose than before administration (14.6 ± 2.8 μU/ml; \( P < 0.05 \)). Insulin concentrations decreased thereafter (75.3 ± 8.2 μU/ml by 15 min, 60.1 ± 8.3 μU/ml by 30 min, 35.7 ± 6.0 μU/ml by 45 min, and 30.6 ± 6.2 μU/ml by 60 min) and returned nearly to the baseline concentration of 15.1 ± 5.3 μU/ml at 2 h (Figure 3). Changes in the group that was administered xylitol were different from those observed for the group receiving glucose; blood insulin increased 11.4 times immediately after the administration (166.7 ± 12.4 μU/ml) and 19.7 times by 15 min after administration (288.0 ± 20.2 μU/ml) compared with baseline values. Blood insulin decreased gradually thereafter, but was still 2.6 times higher than baseline concentrations after 2 h (38.2 ± 13.9 μU/ml).

**Blood Glucose and Insulin Concentrations in Ketotic Cows**

Blood glucose concentrations (Figure 2) increased 8.1-fold from 38 ± 5 mg/dl to 312 ± 18 mg/dl immediately following administration of glucose (\( P < 0.05 \)).

**Figure 4.** Changes in the serum concentrations of free fatty acids, triglycerides, and total cholesterol of ketotic cows after administration of glucose (●) and xylitol (○). Vertical bars represent the standard error of the mean. Asterisk indicates difference (\( P < 0.05 \)) between groups.
administration to 31.6 ± 5.2 μU/ml after 60 min (Figure 3).

Physiological Effects of Xylitol in Ketotic Cows

For the group administered glucose, the free fatty acid concentrations decreased from baseline concentrations (0.36 ± 0.08 meq/L) immediately after administration to 0.29 ± 0.05 meq/L. Mean free fatty acid concentrations then gradually decreased at 15 min (0.22 ± 0.04 meq/L) and 30 min (0.19 ± 0.06 meq/L) (Figure 4). For the group receiving xylitol, free fatty acid concentrations immediately after administration (0.46 ± 0.07 meq/L) were comparable with baseline values. Concentrations decreased thereafter to 0.40 ± 0.05 meq/L by 15 min, 0.37 ± 0.06 meq/L by 30 min, and 0.28 ± 0.05 meq/L by 60 min.

For the group receiving glucose, triglyceride concentrations were similar immediately after or 60 min after the administration (7.4 ± 1.2 mg/dL). Xylitol administration was followed by an immediate increase (16.6 ± 2.0 mg/dL); after 15 min, triglyceride concentrations (32.0 ± 3.5 mg/dL; P < 0.05) were 4.3-fold the baseline concentration. However, the triglyceride concentration decreased to 8.4 ± 1.8 mg/dL after 60 min to near the predadministration concentration. The total cholesterol concentration was unchanged for either group (Figure 4).

The AST concentrations were no different for the group receiving glucose (Figure 4). For the group administered xylitol, AST showed little difference from baseline (120.1 ± 15.6 μU/L) until immediately after administration (115.8 ± 22.2 μU/L), but increased gradually after 15 min and nearly doubled after 60 min (248.2 ± 39.7 μU/L; P < 0.05). The AST concentration was about 1.6-fold higher (191.0 ± 30.4 μU/L) even after 120 min.

The 11-OHCS concentrations (Figure 5) of the group receiving glucose were similar at all times after administration compared with the baseline concentrations (5.1 ± 0.5 μg/dL). For the group receiving xylitol, 11-OHCS increased immediately after administration (6.2 ± 0.6 μg/dL), increased further after 15 min (8.9 ± 1.3 μg/dL), and remained high until after 60 min (8.5 ± 0.6 μg/dL; P < 0.05), but returned to the predadministration concentration by 120 min (6.2 ± 0.4 μg/dL) (Figure 5).

Urinary ketone bodies were observed for all cows at 60 and 120 min after administration of glucose as well as before the administration. Also, feed intake did not return to normal but remained depressed. Urinary ketone bodies were not observed in all cows that received xylitol 60 min after administration, and 3 of 5 cows resumed normal feed consumption.

DISCUSSION

Xylitol is converted to glycogen in the liver, as is glucose, and xylitol has long been used for the treatment of human diabetes because of its potent stimulatory effect on insulin secretion and its antiketogenic effect (7, 23). In the present study, glucose and xylitol were administered to nonketotic and clinically ketotic cows. The physiologic and therapeutic effects of both compounds were compared over time.

The blood glucose concentration increased rapidly for both groups of cows immediately after administration, then decreased gradually, and returned to the predadministration concentration after 120 min. However, when xylitol was administered to the same groups, blood glucose responded differently. Little change was noted immediately after treatment, but mean concentrations increased after 60 to 120 min to nearly 2- to 3-fold higher than those concentrations present before administration.

Nonketotic dogs and humans that received xylitol have been reported to have blood glucose concentrations that did not change or that decreased after
administration of small doses of xylitol (17). However, when dogs were administered xylitol at a high dose (2.5 g/kg), blood insulin increased markedly, and after 90 min, blood glucose also increased markedly (17). In the present study, the blood glucose increased nearly 2-fold from the preadministration concentration to the concentration 120 min after xylitol administration. These slow responses of blood glucose might be a result of reverse conversion of xylitol to glucose via fructose-6-phosphate with gluconate and pentose phosphate pathways (2, 21), temporary accumulation of glucose in the circulation because of the marked increase in glucose-6-phosphate, or promotion of pancreatic glucagon synthesis or adrenocortical corticoid synthesis (17).

The responses of insulin secretion to xylitol administration were 2.2- to 4.9-fold greater than those to glucose administration, and blood insulin increased more markedly for the group receiving xylitol than for the group receiving glucose. This insulin increase might be explained by a decrease in insulin degradation because of the diffusion of xylitol that was not dependent on insulin in peripheral tissues, by stimulation of synthesis and release in the pancreas of insulin, or by both the decrease in degradation and the increase in insulin synthesis.

Ketosis has been associated with the pancreatic B-cell dysfunction (9, 10). The time courses in decreasing rates of blood glucose and insulin concentrations were slower, and the responsiveness of insulin secretion to glucose administration was reduced, for ketotic compared with nonketotic cows. In the present study, the decreasing rates of glucose and insulin concentrations and the responses of insulin secretion to glucose and xylitol were slower and lower in the ketotic than in the nonketotic group.

Free fatty acids and ketones are increased, and triglycerides are decreased, in ketotic cows (3). In this study, free fatty acids gradually decreased in ketotic cows until 60 min after glucose administration. The decrease in free fatty acids after glucose administration was probably due to inhibition of continuous free fatty acid production for glyconeogenesis by the increased blood glucose and insulin concentrations. After xylitol administration, free fatty acids decreased, and triglyceride increased. The decrease in free fatty acids after xylitol administration might be due to reversed generation of blood glucose by the glycolytic system. The marked increase in triglycerides in the xylitol group was thought to have occurred because of increases in the NADH2 or NADPH2 activities that were produced in the conversion of xylitol to D-xylitol in the gluconate pathway (21).

The serum AST is an important diagnostic index in diseases of the liver and the biliary tract. The increase of the serum AST in the group receiving xylitol could not be explained but was considered to have been related to changes in cell membrane permeability following xylitol administration and not caused by the disease. The 11-OHCS, however, was regarded as an index of hormone activities in body fluids and was produced under hypoglycemic conditions by increased release of ACTH. The action of 11-OHCS inhibited glucose metabolism in peripheral tissues and promoted lipid degradation. Production of 11-OHCS was suppressed in hyperglycemic states. Therefore, the decrease in 11-OHCS in the glucose group was considered to be a result of the inhibitory effect of the marked hyperglycemia and increased insulin secretion, and the increase in 11-OHCS by 120 min after administration was considered to have been a reflex rebound elicited by the decline in the blood glucose concentrations. The increase in 11-OHCS was considered to have been caused by activation of NADPH2 production (19) needed for corticoid synthesis, synergism with ACTH, and the lack of inhibition by hyperglycemia relative to the group receiving glucose. Hormone activities were enhanced more in the group receiving xylitol than in the group that was administered glucose.

In the present study, the usefulness of glucose and xylitol administration was evaluated for nonketotic and ketotic cows, and the physiologic effects of xylitol were examined from the responses of the blood glucose and insulin concentrations by ketotic cows. The responses of the blood glucose and insulin concentrations to xylitol administration were better than those to glucose administration. The decrease in free fatty acids, increase in triglycerides, and improvements in clinical signs and symptoms also suggested the usefulness of xylitol administration for the treatment of ketosis.

REFERENCES
GLUCOSE AND XYLITOL TOLERANCE OF COWS


