Evaluation of a Mechanistic Model of Glucose and Lipid Metabolism in Periparturient Cows

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ABSTRACT

A mechanistic model was previously developed to quantitatively describe glucose and lipid metabolism in periparturient cows. The objectives of the current study were to evaluate the accuracy and precision of the model by comparing predictions to data collected in an independent experiment; to identify the critical metabolic processes for ketosis development; and to use the model to evaluate the relative importance of dry matter intake, calf birth weight, milk yield, and body condition score on nutrition management. Residuals (observed – predicted) were regressed on model predictions using the independent data for the model inputs, and prediction error was calculated. Each model parameter (e.g., the rate of glucose consumption by peripheral tissues) was increased independently by 1 standard deviation to identify the critical metabolic processes for ketosis development. Critical control points to prevent ketosis were identified by increasing the driving variables of the model by 1 standard deviation to estimate the response in ketone body formation. The root mean square prediction error was 0.527 mM for ketone body predictions. The sensitivity analysis indicated that in the first few days of lactation, the rate of nonesterified fatty acid utilization had a greater effect on ketone body concentrations in periparturient cows than the other parameters tested in the model. The model was consistent with the knowledge that over-fattening during the prepartum period should be avoided to help prevent ketosis.

Key words: model evaluation, periparturient cow, metabolism

INTRODUCTION

Dairy cows are susceptible to ketosis during the periparturient period. Minimizing the incidence of ketosis requires a comprehensive understanding of the meta-

bolic processes that occur during the periparturient period. The susceptibility to ketosis is associated with many metabolic processes such as fat mobilization, ketone body (KB) utilization, NEFA utilization, and glucose consumption by peripheral tissues. Metabolites in blood vary greatly during the periparturient period. These variations and the interactions make it difficult to identify the contribution of each process to the KB profile.

The incidence of ketosis can usually be decreased through improved nutrition and feeding management. Many factors are involved in the development of ketosis including milk yield, BCS, and DMI (Drackley, 1997). High-producing cows are more susceptible to ketosis than low-producing ones (Baird, 1982). Over-conditioned cows are at greater risk for ketosis than normal cows (Fronk et al., 1980). Other evidence suggests that nutrient intake during early lactation is critical to minimize the incidence of ketosis (Lean et al., 1994). However, these factors are closely interrelated. Cows that have high DMI usually produce more milk. Cows that are fat or overconditioned at calving may be at risk for lower feed intake (Treacher et al., 1986), and lower milk yield (Gearhart et al., 1990). The interrelationships make it difficult to quantify the relative importance of feed intake, body condition, and milk yield to periparturient metabolism in cows.

The objectives of the current study were to evaluate the accuracy and precision of the model (Guo et al., 2008) with data collected in an independent experiment, to identify critical metabolic processes for ketosis development, and to determine the relative importance of DMI, calf birth weight, milk yield, and BCS to nutritional management.

MATERIALS AND METHODS

Data Sets

Independent data from an animal trial by DeFrain et al. (2004) were used to evaluate the accuracy and precision of the model. In the animal trial, 30 Holstein cows were used to evaluate the effects of feeding glycerol from d 14 prepartum to 21 DIM. Treatments were

Received December 18, 2008.

Accepted June 25, 2008.

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0.86 kg/d of corn starch (control), 0.43 kg/d corn starch + 0.43 kg/d glycerol (low glycerol), or 0.86 kg/d glycerol (high glycerol) topdressed and hand-mixed into the upper one-third of the daily ration. There were 2 reasons for the selection of the independent data. First, the independent data challenged the model because the diets differed from those used to develop the model, in which a TMR was fed without topdressing. Nonetheless, the ingredient composition of the control diet was similar to diets widely used on dairy farms. Second, glycerol was added in the other 2 diets in the independent data. Information on the digestion and metabolism of dietary glycerol is limited in dairy cows. Unusual ingredients in the diets could further challenge the model being evaluated.

The following assumptions and conversions were made to transform the independent data into the form of the driving variables and response variables of the model. The rates of propionate and butyrate production from the control diet in the independent data were estimated from feed composition and DMI according to Murphy et al. (1982). Rumen fermentation of glycerol-supplemented diets could not be appropriately estimated by Murphy's model, which was developed for typical diets. Although changes in acetate production were poorly reflected by changes in acetate concentration, production rates of propionate and butyrate were correlated with their respective rumen concentrations (Sharp et al., 1982). The rates of propionate and butyrate production from low- and high-glycerol diets were extrapolated from the control diet by the ratios of VFA concentrations in rumen fluid. It is worth noting that such an extrapolation would further introduce prediction error, the magnitude of which is difficult to determine. In the independent data, glycerol and KB concentrations were not measured. The KB concentrations were estimated by BHBA concentrations and the ratio of KB to BHBA. The ratio was set to 1.18 prepartum and 1.34 postpartum (Guo et al., 2007). The initial value for glycerol concentration was assigned to 0.015 mM, adapted from Guo et al. (2007). The initial values for the rest of the response variables were the pretreatment measurements from the independent data.

The data from the control group in the developmental data set (Guo et al., 2007) were used as reference data for model behavior and sensitivity analysis instead of the independent data for the following reasons. First, the nutrition management for control animals in the developmental data set was different from that in the independent study. Second, glycerol concentrations in plasma were not measured in the independent study. Third, only plasma BHBA was measured in the independent data, not the total KB concentrations.

In the developmental and independent data, body fat content was not actually measured, but was estimated by the equation:

$$\text{Body fat (kg)} = \text{BW} \times 0.817 \\ \times (\text{BCS} \times 7.54 - 3.77)/100,$$

where $\text{BW} \times 0.817$ was the estimate of empty body weight (NRC, 2001); $\text{BCS} \times 7.54 - 3.77$ was derived from Table 2–4 in NRC (2001).

Model Evaluation

The model accuracy and precision were determined by comparing the residuals (observed – predicted) to predicted values. The model-predicted values were calculated from DMI, feed composition, VFA concentrations of rumen fluid, calf birth weights, milk yield, milk composition, BW, and BCS from the independent data. The observed data were the concentrations of blood metabolites and body fat content from the independent data. The accuracy and precision of the model were evaluated by the root mean square prediction error (RMSPE; Bibby and Toutenburg, 1977):

$$\text{RMSPE} = \sqrt{\frac{\sum(\text{observed} - \text{predicted})^2}{n}}.$$

A mean bias for model predictions was declared if mean of residual (observed – predicted) values was significantly different from zero. Linear bias for model predictions was evaluated by regression analysis of residuals against model predictions. Statistical analysis was performed with PROC REG (SAS Institute, 1999). Statistical significance was declared at $P < 0.05$.

We evaluated how sensitive the model was to estimates of model parameters by changing each parameter by 1 standard deviation. The values for the model parameters and the standard deviation associated with them were adapted from the reference data (Guo et al., 2008). The model responses of fat loss and the area under the curve (AUC) for blood metabolites were evaluated to identify the key parameters that have a great effect on the response variables of the model. The AUC was calculated by using the trapezoidal rule (Jones, 1997).

The behavior of the model was observed when DMI, calf birth weight, milk yield, or BCS were increased by 1 standard deviation. The standard deviations were adapted from the reference data. The body fat loss and blood metabolite changes in the AUC across the last 21 d prepartum and the first 21 d postpartum were

Table 1. Model evaluation for accuracy and precision by the independent data¹

Prediction ²	n	Mean ³	RMSPE ⁴	CV, %	Mean bias		Linear bias		Residual error, ⁵ %
					Bias ⁶	Error, ⁷ %	Bias ⁸	Error, ⁹ %	
Glucose, mM	153	4.3	1.00	24	-0.62**	38.8	-1.02**	24.5	36.7
NEFA, mM	134	0.39	0.238	60	-0.037	2.5	0.370	1.7	95.8
KB, mM	137	0.65	0.527	81	-0.373**	50.1	-0.515	1.0	48.9
Fat, kg	47	119	7.4	6	-1.4	3.6	-0.03	1.3	95.1

¹The independent data were adapted from DeFrain et al. (2004).

²Plasma concentrations of glucose, NEFA, and ketone bodies (KB).

³Mean of model predictions.

⁴Root mean square prediction error = square root of $[\Sigma (\text{observed} - \text{predicted})^2/n]$; Bibby and Toutenburg (1977).

⁵Percentage of total prediction error not explained by mean and linear bias.

⁶Mean observation – mean prediction.

⁷Percentage of total prediction error explained by mean bias = $n \times \text{mean bias}^2 / \Sigma (\text{observed} - \text{predicted})^2 \times 100\%$.

⁸Slope of residual on prediction.

⁹Percentage of total prediction error explained by linear bias = $\text{linear bias}^2 \times \Sigma [\text{predicted} - \Sigma (\text{predicted})/n]^2 / \Sigma (\text{observed} - \text{predicted})^2 \times 100\%$.

** $P < 0.01$.

compared with the reference data and were evaluated to ensure that the model contained the provisions adequate for simulation of response relationships observed in actual animal studies.

RESULTS AND DISCUSSION

Residual Analysis

The RMSPE for glucose predictions was 1.00 mM, which was 24% of mean prediction (Table 1). The variation could result from many factors such as stress, glucocorticoid, and adrenergic agents (Bell, 1995), which are not considered in the model. The model overestimated ($P < 0.01$) plasma glucose concentrations by 0.62 mM, accounting for 38.8% of total prediction error. The difference in feed composition between the trial for model development and model evaluation may cause different patterns in rumen fermentation. However, the coefficients from model of Murphy et al. (1982) had been used to estimate VFA production, which may result in the mean bias for glucose predictions. A linear bias was also observed ($P < 0.01$) for the glucose predictions (Figure 1), accounting for 24.5% of total prediction error (Table 1). This linear bias may have resulted from feed intake as the glucose residuals were negatively related to DMI ($P < 0.01$, Figure 2). In the independent trial, starch, glycerol, or both were top dressed with the TMR, which may cause a pulse in NSC digestion. Consequently, as feed intake increased, more starch may escape from the rumen fermentation and end up in the small intestine. It had been reported that infusion of starch directly into the small intestine did not increase glucose appearance

in the portal-drained viscera (Nocek and Tamminga, 1991). The starch that disappears in the small intestine may be utilized by the portal-drained viscera such as intestinal enterocytes and mesenteric and omental fat depots (Reynolds, 2006). This utilization could result in overprediction for plasma glucose concentrations by the model as DMI increased and more starch reached the intestine. However, information on glycerol digestion via topdress supplementation was not available.

There were no linear and mean biases observed in NEFA predictions ($P > 0.05$). The RMSPE for NEFA and KB predictions were 0.238 and 0.527 mM, which were 60 and 81% of mean prediction, respectively. In the model, the KB compartment was downstream to the NEFA compartment, which was downstream to the glucose compartment. The prediction error from the upstream compartments could pass downward and accumulate in downstream compartments resulting in relatively high prediction errors associated with NEFA and KB. The model overpredicted KB concentrations by 0.373 mM ($P < 0.01$, Table 1). The same reason for overestimating glucose predictions may also be responsible for the main bias for KB as discussed previously. In addition, the independent experiment used glycerol as a dietary constituent, which may have profound effects on glucose and energy metabolism in the cows. Little is known about fermentation and metabolism of glycerol in the rumen. A different analysis method was used to determine BHBA concentrations in the independent data set from that used in the development data set. The KB concentrations in the independent data set were not measured directly, but were estimated from the ratio of BHBA to acetoacetate and acetone, which would contribute to some of the error.

The RMSPE for body fat prediction was 7.4 kg, which was 6% of mean prediction (Table 1). No bias was observed for body fat predictions ($P > 0.05$; Figure 1). The residuals for glucose, NEFA, and KB concentrations and body fat content were similarly distributed among the treatment groups, which were the control, high-glycerol, and low-glycerol groups in the independent study (Figure 1). The similarity of the residual distributions indicated that the model applied reasonably well to the situation in which dietary glycerol was fed and explained most treatment effects in the independent study.

Sensitivity Analysis

The goal of sensitivity analysis is to identify the key control points in glucose and lipid metabolism contributing to the development of ketosis. The rate of glucose utilization by peripheral tissues had a greater effect on the glucose concentrations in plasma than body fat mobilization rate (Figure 3). Glucose concentrations

are affected by the rate of fat mobilization in a relatively indirect way compared with the rate of glucose utilization by peripheral tissues. A high lipolysis rate may increase mitochondrial NADH and contribute more energy to the cellular energy charge, resulting in reduced demand for energy from glycolysis (Spriet and Watt, 2003).

Although the rate of fat mobilization is the main factor affecting glycerol concentrations (Figure 3) and fat loss (Table 3) during the periparturient period, an increased rate of glucose utilization by peripheral tissues could also result in elevated glycerol concentrations in the first few days of lactation (Figure 3). Uptake of plasma glucose by peripheral tissue is related to insulin concentration, tissue sensitivity to insulin (Pettersen et al., 1993), and glucose concentration (Yki-Jarvinen et al., 1987). Tissue sensitivity to insulin is defined as the insulin concentration required to produce a half-maximal response (Kahn, 1978). In the peripheral tissues of late-pregnant ewes, the insulin concentrations required to produce a half-maximal response increased,

Figure 1. Residual analysis for model prediction. Plot of residuals (observed – predicted) against model predictions. The residuals from each treatment group in the independent study were ■ = control, Δ = high-glycerol, and ◊ = low-glycerol groups. The horizontal line represents mean bias and the other line represents linear bias. Absence of a horizontal line indicates that mean bias is not different from zero ($P > 0.05$). Glucose: mean bias $Y = -0.62$ ($P < 0.01$); linear bias $Y = 3.73 - 1.02X$ ($P < 0.01$), NEFA: mean bias $Y = -0.037$ ($P = 0.07$); linear bias $Y = -0.183 + 0.370X$ ($P = 0.13$); ketone bodies: mean bias $Y = -0.373$ ($P < 0.01$); linear bias $Y = -0.037 - 0.515X$ ($P = 0.10$); body fat: mean bias $Y = -1.4$ ($P = 0.20$); linear bias $Y = 2.54 - 0.03X$ ($P = 0.43$).

Figure 2. Plot of glucose residuals (observed – predicted) against DMI. The residuals from each treatment group in the independent study were ■ = control, Δ = high-glycerol, and □ = low-glycerol groups. $Y = 0.374 - 0.035X$ ($P < 0.01$).

but the maximal response remained relatively unchanged (Pettersson et al., 1993). Accordingly, in spite of insulin resistance, a great amount of glucose could be utilized by peripheral tissues if the concentrations of insulin and glucose were elevated.

Plasma NEFA could be oxidized or converted to KB by the liver, reesterified to triglyceride in lipid tissue, or incorporated into milk fat in mammary gland. Thus, the concentrations of plasma NEFA are greatly affected

by NEFA utilization rate. The effect of fat mobilization rate and peripheral glucose consumption rate on NEFA was similar to that on glycerol (Figure 3).

The model simulation demonstrated that plasma KB concentrations are dependent mainly upon fat mobilization and KB utilization rates postpartum (Table 3). All but a few tissues such as liver and brain can use KB because of the presence of BHBA dehydrogenase. The impact of fat mobilization rate on KB before parturition is not as intensive as that after parturition (Table 3) because fatty acids from lipolysis are not the main source of prepartum KB (Katz and Bergman, 1969). The susceptibility to ketosis is not only dependent on total exposure to KB during a period as measured by the AUC, but also on the maximal concentrations of KB the animal suffers. The results of model simulation indicated that the peak of KB concentrations in the first few days of lactation could also be affected by NEFA utilization rate (Figure 3). Therefore, the susceptibility to ketosis is closely related to the rate of NEFA utilization in the first few days of lactation.

Behavioral Analysis

An analysis was performed to ensure the model is capable of simulating the response relationships observed in studies and to compare the importance of different factors on the animal response. The concentrations

Figure 3. The effect of increasing model parameters by 1 standard deviation on plasma metabolites. — = control; Δ = increased rate of NEFA utilization; ○ = increased rate of fat mobilization; □ = increased rate of glucose consumption by peripheral tissues; × = increased rate of ketone body utilization. The control was adapted from Guo et al. (2007). The standard deviations were adapted from Guo et al. (2008). Absence of a parameter in a panel indicates that the parameter is positioned downstream, and thus, has no impact on that model output.

Table 2. Model responses to the increased DMI, calf weight, milk yield, and BCS

Item	Change in driving variable ¹ (%)	Predicted responses of AUC for blood metabolites and fat loss ² (%)				
		Glucose	Glycerol	NEFA	KB ³	Fat loss
Prepartum ⁴ DMI	15.6	3.5	-1.5	-0.8	3.2	-4.6
Calf weight	10.8	-1.0	0.4	0.2	0.1	1.1
Prepartum BCS	22.3	0.3	21.8	18.1	10.9	23.3
Postpartum ⁵ DMI	9.8	4.2	-3.1	-2.4	0.2	-3.5
Milk yield	12.7	-4.3	3.1	2.3	1.7	3.5
Postpartum BCS	22.3	0.4	20.3	13.6	9.1	23.1

¹Increased by 1 standard deviation. The standard deviations were adapted from Guo et al. (2008).

²AUC = area under the curve; the model responses were expressed as a percentage change in response variables compared with the reference data.

³Plasma ketone bodies.

⁴Prepartum = the last 21 d of gestation.

⁵Postpartum = the first 21 d of lactation.

of plasma KB were positively related to fetal weight, milk yield, and BCS (Table 2). These model responses were consistent with published results indicating that overconditioned cows are at high risk of ketosis development (Fronk et al., 1980), and that cows with high milk production are at high risk of ketosis development (Drackley, 1997).

The 22.3% increase in the initial BCS at calving had little effect on plasma glucose concentrations. However, glucose concentrations were positively related to DMI and negatively related to fetal weight and milk yield (Figure 4). The model responses to a 9.8% increase in postpartum DMI and a 12.7% increase in milk yield were changes of 4.2 and 4.3% in glucose AUC, respectively (Table 2). The similar magnitudes of the model responses to DMI and milk yield implied that DMI and milk yield have a similar effect on the plasma glucose concentrations during the periparturient period. The

response of fat loss to DMI and milk yield was similar to that of glucose. The model response of glucose concentrations to fetal weight was not as intense as it was to milk yield. The lower intensity of the prepartum response is consistent with the fact that most hypoglycemia is developed postcalving in cows, not before parturition, in contrast to the occurrence of hypoglycemia in sheep.

The initial BCS at calving had a greater impact on plasma glycerol concentrations compared with DMI, fetal weight, and milk yield. A similar effect was observed on NEFA, KB (Figure 4), and body fat loss postpartum (Table 2). The behavior analysis of initial BCS mimics overfeeding during the prepartum period, which usually leads to deposition of body fat and overcondition at calving (Fronk et al., 1980; Grummer et al., 1995). Fat cows are prone to increased adipose sensitivity, which is the tendency to mobilize body fat

Table 3. The impact of increasing the model parameters on area under the curve (AUC) for blood metabolites and body fat loss

Parameter ¹	Change in parameter, % ²	Predicted responses of AUC for blood metabolites and fat loss ³ (%)				
		Glucose	Glycerol	NEFA	Ketone bodies	Fat loss
Prepartum ⁴ U _(peri, glucose)	42.6	-7.7	0.5	0.3	0.1	1.5
Prepartum P _(fat, adipose)	48.7	0.1	15.0	7.8	2.5	46.5
Prepartum U _(NEFA)	42.0	NA ⁶	NA	-23.8	6.0	NA
Prepartum U _(KB)	38.8	NA	NA	NA	-25.2	NA
Postpartum ⁵ U _(peri, glucose)	65.3	-7.8	5.3	4.1	3.1	6.0
Postpartum P _(fat, adipose)	40.3	0.6	29.2	20.0	13.7	33.0
Postpartum U _(NEFA)	34.7	NA	NA	-21.7	3.0	NA
Postpartum U _(KB)	35.4	NA	NA	NA	-23.8	NA

¹U_(peri, glucose) = utilization rate of glucose by peripheral tissues (mol/d per kg of BW^{0.75}); T_(fat, adipose) = turnover rate of adipose tissues before 7 d prepartum (kg/d per kg of body fat); P_(fat, adipose) = mobilization rate of fat from adipose tissues (kg/d per kg of body fat); U_(NEFA) = utilization rate of NEFA (mmol/d per mM NEFA concentration); and U_(KB) = utilization rate of KB (mmol/d per mM KB concentration).

²Increased by 1 standard deviation. The standard deviations were adapted from Guo et al. (2007).

³The model responses were expressed as a percentage change in response variables compared with the reference data.

⁴Prepartum = the last 21 d of gestation.

⁵Postpartum = the first 21 d of lactation.

⁶NA = impact of the parameter was not considered in the model.

Figure 4. Model responses to increasing DMI, calf weight, milk yield, and BCS by 1 standard deviation. — = control; Δ = increased DMI; $\circ$ = increased calf weight/milk yield; $\square$ = increased BCS. The control and standard deviations were adapted from Guo et al. (2007).

rapidly under stresses such as calving or underfeeding (Oetzel, 2003). The results of BCS behavior analysis are in agreement with the observation that fat cows usually have a high concentration of blood NEFA and BHBA (Fronk et al., 1980). Fat mobilization releases NEFA as well as glycerol. Excessive mobilization of fat not only increases concentrations of NEFA (Rukwamsuk et al., 1999) and KB (Oetzel, 2003), but also increases glycerol concentrations as predicted by the model. In addition, ketosis is observed more frequently in fat cows than in normal cows (Andrews et al., 1991). Thus, the model simulation indicates that it is important to avoid overfattening during the prepartum period to prevent ketosis.

Before parturition, cows were in a positive energy balance, and most of KB was likely produced by rumen epithelia from feed fermentation (Katz and Bergman, 1969). The KB from feed fermentation could result in a positive relationship between KB concentrations and DMI. This relationship is in agreement with the result that the AUC for KB was positively related to DMI during the prepartum period (Table 2; Figure 4). After parturition, this relationship is attenuated by adipose mobilization. As DMI increased after parturition, less body fat was mobilized and less KB was produced from incomplete fatty acid oxidation. In the model, the importance of DMI, fetal weight, milk yield, and BCS was evaluated partially. The interaction among the 3 was not considered in the behavior analysis.

Limitations and Applications

The model assumed that glucose deficiency promoted fat mobilization in periparturient cows in excess of negative energy balance. The robustness of the model relies on the accurate estimates of glucose supply to the system. Murphy's model (Murphy et al., 1982) had been used to estimate glucose supply from rumen fermentation. However, this model is empirical and does not include some factors that affect rumen fermentation such as feeding regimen, particle size, and physical stage. Therefore, the estimates of glucose supply into the model are associated with unknown variation.

In the developmental and independent data, body fat content was estimated from BCS and empty BW (NRC, 2001). In early lactation, body reserves are mobilized to compensate for nutrient imbalance. At the same time, the proportion of visceral tissues is increased to adapt to the increasing DMI. Thus, empty BW could not be accurately estimated by $BW \times 0.817$ during this period. In addition, BCS is a subjective measurement and always associated with human error. Different methods for BCS measurements are used in the field. The BCS was measured according to Edmonson et al. (1989) in the data for model development, whereas the method of Wildman et al. (1982) was used in the independent data. Therefore, the absolute values for body fat loss should be used cautiously although the quantitative changes predicted by the model were within a reasonable range.

The results of sensitivity analysis highlighted some potential insights into the underlying mechanism of ketosis development for further investigation. For example, the model demonstrated that the maximum concentration of blood KB is sensitive to the rate of NEFA utilization, which regulates the amount of blood NEFA entering ketogenesis in the liver and oxidation in muscle. Thus, the model implies that the peak of KB concentrations in the first few days of lactation could be decreased either by inhibiting ketogenesis in the liver or by enhancing NEFA oxidation in muscle. Future studies in these areas could lead to a decrease in the incidence of ketosis by improving dietary management during the periparturient period.

CONCLUSIONS

Overall, the model is valuable for studying the homeorhetic state of glucose and lipid metabolism in periparturient cows. The profiles of blood metabolites could be simulated and evaluated under various circumstances such as different production levels, feed intakes, and initial BCS at calving. The model evaluation indicated that the ability to utilize NEFA had a great effect on susceptibility to ketosis during the first few days of lactation. It is important to avoid overfattening in late-gestation period.

ACKNOWLEDGMENT

The authors thank J. M. DeFrain, A. R. Hippen, and collaborators (South Dakota State University, Brookings) for supplying data.

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