EVALUATION OF THE BOLIE MODEL DESCRIBING BLOOD GLUCOSE RESPONSE FOR THE APPLICATION TO CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

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In an attempt to develop an appropriate infusion program in a continuous subcutaneous insulin infusion system, a conventional pharmacodynamic model (the Bolie model) for describing the relationship between blood glucose and serum insulin levels was evaluated, using a depancreatized dog preparation. The Bolie model was found useful in estimating the basal insulin infusion rate. However, the model could not predict the serum insulin concentration–time profile required to maintain the postprandial blood glucose levels within a physiological range. It will be necessary to develop a more appropriate model for determining the prandial subcutaneous insulin infusion rates in the continuous subcutaneous insulin infusion system.

Keywords — insulin; pharmacodynamic model; Bolie model; basal insulin infusion; prandial insulin infusion; dog

INTRODUCTION

Recently, Pickup et al.1-3) and other investigators 4-6) employed a preprogrammable insulin-delivery system in which insulin was administered via the subcutaneous route with a portable infusion pump (continuous subcutaneous insulin infusion system: CSII system). The technique employs a continuous infusion of insulin at basal rates designed to hold the blood glucose concentration within the normal range in the overnight fasted state, with empirically determined supplementary infusions being given before meals. As compared to previous subcutaneous insulin injection therapy, the CSII system can greatly improve blood glucose and metabolic profiles.7-10)

In the CSII system, the insulin infusion program is determined by an empirical or trial-and-error method. Diabetic therapy using the CSII system will be improved by developing a rational method of determining the required insulin infusion program. An approach to optimize diabetic therapy with the CSII system involves determination of the insulin concentration–time profile required to maintain the diurnal blood glucose concentration within the physiological range. The subcutaneous insulin infusion pattern to reconstruct this insulin concentration–time profile must then be calculated. We have already developed a method for reconstructing a predetermined serum insulin concentration pattern using the CSII system.11)

In the present study, we have evaluated a conventional pharmacodynamic model, which describes the relationship between blood glucose and serum insulin concentrations, using a depancreatized dog to provide a basis for developing an appropriate subcutaneous insulin infusion program.

MATERIALS AND METHODS

Animal — One male beagle dog (body weight: 9 kg) was depancreatized under anesthesia with pentobarbital sodium (50 mg/kg, i.v.)
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after an overnight fast. The dog was allowed unrestricted access to water, and a dose of 3.0 g of pancreatin (Beryzym, Shionogi Pharmaceutical Co., Japan) and 150 g of dog-food (CD-5, Clea Co., Japan) were given twice a day. A control period, of about one week after the pancreas had been removed, was needed before the initiation of experiments. No immunoreactive serum insulin was detected and the blood glucose concentration was about 450 mg/dl, just prior to the first experiment. During a resting period from one experiment to another (1–12 weeks), single daily subcutaneous injections of equal amounts (<8 U) of Actrapid MC® and Monotard MC® (Novo Industri., Copenhagen) were given to the depancreatized dog to control the high blood glucose. Dose adjustment were made based on the overnight fasting blood glucose levels.

**Insulin Infusion Pump** — A battery-powered preprogrammable continuous infusion pump (126 × 70 × 26 mm, 270 g, Terumo Co., Japan) was used. The infusion system was fitted with a finger pump and programmed at rates ranging from 0.02 to 2 ml/h, by a programmable speed setting with 100 steps. The infusion rates were set at 15-min intervals.

**Single Bolus Subcutaneous Injection** — Single bolus subcutaneous injections of 1, 1.5, 2 and 3 units of insulin (Actrapid MC, Novo Industri., Copenhagen) were given to the depancreatized dog with a 100-μl microsyringe over a three-month period. Under conditions of starvation and absence of exogeneous insulin, the insulin injection was made in the subcutaneous tissue of the anterior abdominal wall in the right or left subcostal region at 9:00 a.m. Blood samples (2 ml each) were withdrawn into 2-ml syringe via a 23 Gage (G) × 1 1/2 needle from the forearm vein just prior to and at 10, 15, 30, 45, 60, 80, 100, 120, 140, 160, 180, 210 and 240 min for measurement of glucose and insulin and at 5, 6, 7, 9, 11 and 24 h for measurement of glucose only after each subcutaneous insulin injection.

**Basal Continuous Subcutaneous Infusion** — Basal continuous subcutaneous insulin infusion was performed on the same depancreatized dog during a two-month period. One ml of 40 U/ml insulin solution was diluted with saline solution to a concentration of 1 U/ml. The diluted insulin was continuously infused throughout the two-month period and delivered via a 23 G × 5/8 butterfly needle into the subcutaneous tissue of the abdominal wall in the right or left subcostal region by the insulin infusion pump. The needle was replaced every 24 to 48 h. The basal insulin infusion rates ranged from 1.33 to 3.64 mU/min. A dose of 5 units of insulin (Actrapid MC) and 200 g of dog-food were given at 9:00 a.m. and 2 units of insulin (Actrapid MC) and 100 g of dog-food at 3:00 p.m. In the overnight fasted state, blood samples (2 ml each) were withdrawn into a 2-ml syringe via a 23 G × 1 1/2 needle placed in the forearm vein just prior to the ingestion of dog-food at 9:00 a.m. the next morning. When the insulin infusion rate was changed, a control period of one or two days was needed before the next blood sampling.

**Glucose Concentration Time Profile after Ingestion of Dog-Food with Basal Insulin Infusion** — On the previous day of the meal ingestion study, the basal insulin infusion was started at 9:00 p.m. to deliver diluted insulin (1 U/ml) at a slow rate of 3.33 mU/min via a 23 G × 5/8 butterfly needle inserted into the abdominal wall. This provided an overnight run-in period, during which the blood glucose was brought into the normal range for the start of the meal ingestion study the following morning. The dog was given 150 g of dog-food at 9:00 a.m. while the basal insulin infusion was continued, and blood samples (1 ml each) were withdrawn into a 1-ml tuberculin syringe via a 23 G × 1 1/2 needle placed in the forearm vein just prior to and at 30, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 540 min after ingestion of dog-food.

**Glucose Concentration Time Profile after an Intravenous Bolus Injection of Glucose with Basal Insulin Infusion** — Under the conditions of the basal insulin infusion mentioned above, 5 g of glucose (10 ml of 50 w/v% glucose solution) was given as a single bolus injection into the forearm vein, and blood samples (1 ml each) were with-
drawn into a 1-ml tuberculin syringe via a 23 G × 1 1/2 needle placed in the forearm vein just prior to and at 10, 20, 30, 45, 60, 90 and 120 min after the injection.

Prandial Continuous Subcutaneous Infusion — The theoretically determined prandial insulin infusion program was applied to the dog at 8:45 a.m. after maintaining the blood glucose level within the physiological range in the overnight fasted state by the basal insulin infusion into the tissue of subcutaneous abdominal wall at a rate of 3 mU/min. One ml of the 40 U/ml insulin solution diluted with saline solution to a concentration of 3 U/ml was delivered via a 23 G × 5/8 butterfly needle into the subcutaneous tissue of the anterior abdominal wall. The dog was given 150 g of dog-food at 9:00 a.m., and blood samples (2 ml each) were withdrawn into a 2-ml syringe via a 23 G × 1 1/2 needle placed in the forearm vein at 8:45, 9:00, 9:30, 10:00, 10:30, 11:00, 11:30, 12:00, 13:00, 14:00, 15:00, 16:00 and 17:00 for measurements of insulin and glucose concentration.

Assay — The blood glucose concentration was measured by the glucose-oxidase method (Glucose-B-Test, Wako Chemical Co., Japan) and the serum immunoreactive insulin concentration by the double antibody method using Insulin RIA Kit® (Dinabot Radioisotope Laboratory, Japan).

Theoretical — In an attempt to use a simplified model applicable for determining the CSII program, a mathematical model described by Bolie and Ackerman et al. (the Bolie model) was used to relate the blood glucose response to the subcutaneous insulin injection. The assumptions on which the Bolie model is based are: 1) The liver, pancreas, and peripheral tissues are in communication with each other via a single compartment, and glucose and insulin are distributed rapidly and uniformly. 2) Glucose disappearance is linearly dependent on the serum insulin concentration and insulin secretion from pancreas is linearly dependent on the blood glucose concentration. These assumptions lead to the following system of differential equations of the first order.

\[
\frac{dg}{dt} = -\alpha \cdot g - \beta \cdot i + G_p \quad \ldots 1
\]

\[
\frac{di}{dt} = -k \cdot i - k_{sec} \cdot g + I(t) \quad \ldots 2
\]

where \( g \) and \( i \) are the blood glucose and insulin concentrations, respectively, and \( \alpha, \beta, k \) and \( k_{sec} \) are the first order rate constants. \( G_p \) and \( I(t) \) are the rate of endogeneous glucose production and the rate at which exogeneous insulin enters the general circulation, respectively.

Figure 1 shows the 24-h blood glucose concentration time profile under the conditions of starvation and the absence of exogeneous insulin in the depancreatized dog used in the present study. The blood glucose concentration was apparently maintained at a high steady-state level under these conditions. Eq. 1 is therefore expressed as,

\[
\frac{dg}{dt} = -\alpha \cdot g_m + G_p = 0 \quad \ldots 3
\]
where $g_{ss}$ refers to the average steady-state glucose level.
Rearranging Eq. 3 to solve for $G_p$,

$$G_p = \alpha \cdot g_{ss} \quad \ldots 4$$

Substituting $\alpha \cdot g_{ss}$ for $G_p$ in Eq. 1,

$$\frac{dg}{dt} = \alpha \cdot (g_{ss} - g) - \beta \cdot i \quad \ldots 5$$

Since the dog used in the present study was totally depancreatized, there was no endogeneous insulin secretion and $k_{sec} \cdot g$ in Eq. 2 may then be set to zero. If the insulin injected to the subcutaneous site ($A_s$) is lost only by the first order absorption process ($k_a$), a differential equation for the change of insulin in the subcutaneous site is,

$$\frac{dA_s}{dt} = -k_a \cdot A_s \quad \ldots 6$$

Furthermore, $I(t)$ in Eq. 2 becomes $k_a \cdot A_s / V$ and the following differential equation results,

$$\frac{di}{dt} = -k \cdot i + k_a \cdot A_s / V \quad \ldots 7$$

where $A_s$ and $V$ are the amount of insulin in the subcutaneous site and the apparent volume of distribution of insulin in the body, respectively.

Solving for the glucose ($g$) and the insulin concentration ($i$) by using Eqs. 5, 6 and 7,

$$i = \frac{F \cdot k_a \cdot D}{V(k_a - k)} (e^{-k \cdot t} - e^{-k_a \cdot t}) \quad \ldots 8$$

$$g = -\frac{F \cdot \beta \cdot k_a \cdot D}{V(k_a - k)(\alpha - k)} e^{-k \cdot t} \quad \ldots 9$$

where $F$, $D$ and $g_p$ are the bioavailability of insulin injected, the amount of insulin injected and the blood glucose concentration just prior to the experiment, respectively.

The fitting of the above model to the actual data was performed on a microcomputer (PC-8001, NEC Co., Japan) using the nonlinear least squares technique. Using Eq. 8, the pharmacokinetic parameters $k_a$, $k$ and $V$ were estimated by the computer using the MODFIT program.\textsuperscript{10} The fitted values for $\alpha$ and $\beta$ were obtained by the steepest descent method using Eq. 9. These analyses assumed complete insulin absorption ($F = 1$) and the parameter value used for $g_{ss}$ was 364 mg/dl, which was an average blood glucose level 24 h after insulin injection in the four single bolus subcutaneous injection experiments.

RESULTS AND DISCUSSION

Published models for describing the relationship between the blood glucose and serum insulin concentrations have usually been classified into two distinct model classes, i.e., a comprehensive model and a simple model. Comprehensive models attempt to deal with the knowledge of metabolic regulation using complicated models with a large number of model parameters.\textsuperscript{17–19} Without extensive experimental investigation for a single individual, it is not possible to estimate parameter values in the comprehensive model. Simple models, on the other hand, do not attempt to library the physiology of metabolism and the experimental manipulation to estimate parameter values can be performed in a routine clinical setting with minimal patient risk.\textsuperscript{12,20,21}

Predictability Based on the Bolie Model in the Single Bolus Subcutaneous Insulin Injection Study

Figures 2 and 3 show the blood glucose and serum insulin concentration vs. time curves obtained after single bolus subcutaneous injections of insulin to the depancreatized dog. Table 1
summarizes the optimal fitted values for the parameters in Eqs. 8 and 9 in each bolus injection experiment. Assuming that insulin was absorbed completely from the subcutaneous tissue, the insulin clearance varied from 0.273 to 0.343 l/min. The average parameter values for $\alpha$ and $\beta$ were $0.0046 \pm 0.0013$ min$^{-1}$ and $0.064 \pm 0.018$ mg/$\mu$U/min/10$^2$, respectively.

As exemplified in Fig. 4, the ability of the computed curves to simultaneously fit the experimental data for the time course of the blood glucose and serum insulin concentrations was clearly demonstrated in each individual experiment. This means that in originally selecting a mathematical model the model used may be considered to be appropriate to describe the blood glucose response to the absorption and disposition kinetics of subcutaneously injected insulin.

In order to examine whether or not the employed model possesses a good predictability, the model parameters $\alpha$ and $\beta$ obtained from the 3-unit subcutaneous insulin bolus were applied for fitting the observed data from the 1, 1.5 and 2-unit insulin injection experiments to Eqs. 8 and 9. The pharmacokinetic parameter values for $k_a$, $k$ and $V$ were those obtained from each individual insulin injection experiment. It was found that the predicted glucose concentration profiles based on the single 3-unit bolus insulin injection data fitted sufficiently well with the actual data from the other single bolus insulin injection experiments (see Fig. 5). These results sug-

![Graph showing blood glucose levels over time](image1)

**FIG. 2.** Time Profile of the Blood Glucose Concentration Resulting from 1 (○), 1.5 (○), 2 (■) and 3 (□) Units Subcutaneous Insulin Injections to a Depancreatized Dog

![Graph showing serum insulin concentrations over time](image2)

**FIG. 3.** Time Profile of the Serum Insulin Concentration Resulting from 1 (○), 1.5 (○), 2 (■) and 3 (□) Units Subcutaneous Insulin Injections to a Depancreatized Dog

**TABLE I.** Pharmacokinetic-Pharmacodynamic Parameters in a Depancreatized Dog

<table>
<thead>
<tr>
<th>Dose (units)</th>
<th>$k_a$ (min$^{-1}$)</th>
<th>$k$ (min$^{-1}$)</th>
<th>$V$ (l)</th>
<th>CL (l/min)</th>
<th>$\alpha$ (min$^{-1}$)</th>
<th>$\beta$ (mg/$\mu$U/min/10$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.098</td>
<td>0.014</td>
<td>24.5</td>
<td>0.343</td>
<td>0.0062</td>
<td>0.040</td>
</tr>
<tr>
<td>1.5</td>
<td>0.036</td>
<td>0.027</td>
<td>10.1</td>
<td>0.273</td>
<td>0.0048</td>
<td>0.084</td>
</tr>
<tr>
<td>2</td>
<td>0.045</td>
<td>0.030</td>
<td>10.8</td>
<td>0.324</td>
<td>0.0033</td>
<td>0.068</td>
</tr>
<tr>
<td>3</td>
<td>0.025</td>
<td>0.014</td>
<td>24.5</td>
<td>0.343</td>
<td>0.0039</td>
<td>0.064</td>
</tr>
<tr>
<td>Mean</td>
<td>0.051</td>
<td>0.021</td>
<td>17.5</td>
<td>0.321</td>
<td>0.0046</td>
<td>0.064</td>
</tr>
<tr>
<td>±S.D.</td>
<td>0.032</td>
<td>0.0085</td>
<td>8.12</td>
<td>0.0286</td>
<td>0.0013</td>
<td>0.018</td>
</tr>
</tbody>
</table>
gested that the employed model was able to characterize the relationship between the serum insulin and blood glucose concentrations after a single bolus subcutaneous insulin injection.

**Prediction of Serum Insulin and Blood Glucose Concentrations in the Overnight Fasted State during Basal Continuous Insulin Infusion**

In the basal insulin infusion experiment, the serum insulin and blood glucose concentrations were at steady-state in the overnight fasted state, since insulin was infused subcutaneously at a certain constant rate during the night. Equation 5 may then be expressed as,

\[ \alpha \cdot (g_{ss} - g_t) - \beta \cdot i_t = 0 \quad \ldots 10 \]

where \( g_t \) and \( i_t \) are the blood glucose and serum insulin concentrations after the overnight fasted state, respectively. Rearranging the above equation to solve for \( i_t \),

\[ i_t = \frac{\alpha}{\beta} (g_{ss} - g_t) \quad \ldots 11 \]

Figure 6 shows the relationship between the blood glucose and serum insulin concentrations after the overnight fasted state during the basal insulin infusion experiment. The solid lines were drawn on the basis of Eq. 11 using the parameter values for \( \alpha \) and \( \beta \) obtained from the 1, 1.5, 2 and 3-unit insulin injection study. Except in the case of using parameter values for \( \alpha \) and \( \beta \) obtained from the one-unit insulin injection experiment, the simulation line based on Eq. 11 provided a good predictability for estimating the fasting insulin and glucose levels. It seemed possible that the deviation in the one-unit insulin

![Graph](image)

**FIG. 4.** *Simulation Curves for the Serum Insulin and Blood Glucose Concentration Profiles Following 3 Units Subcutaneous Insulin Injection*

The solid lines represent the estimated values using Eqs. 8 and 9. Key: (●), measured glucose concentration; (○), measured insulin concentration.

![Graph](image)

**FIG. 5.** *Simulation Curves for the Serum Insulin and Blood Glucose Concentration Profiles Following 1, 1.5 and 2 Units Subcutaneous Insulin Injections*

The simulation lines for serum insulin concentration were based on the parameter values estimated from each individual insulin injection experiment. The simulation lines for blood glucose concentration were based on the fixed values for \( \alpha \) and \( \beta \) obtained from the 3-unit insulin injection experiment. Key: (●), measured glucose concentration; (○), measured insulin concentration.
injection was due to the insufficient insulin effect on the blood glucose, resulting in the inaccurate estimate of the parameter values for $\alpha$ and $\beta$. In other words, Eq. 11 can well predict the relationship between the serum insulin and blood glucose concentrations in the overnight fasted state during the basal continuous subcutaneous insulin infusion in the CSII system, as long as the appropriate parameter values for $\alpha$ and $\beta$ are obtained from a single bolus subcutaneous insulin injection experiment in which the glucose response is large enough to estimate the parameter values.

**Prandial Continuous Subcutaneous Insulin Infusion**

A time course of blood glucose concentrations after ingestion of dog-food (150 g) during the basal insulin infusion is shown in Fig. 7. Under the same conditions of basal insulin infusion, a bolus intravenous injection of glucose (5 g) was given to the same dog on separate occasions and semilogarithmic plots of the blood glucose concentration above the initial level versus time are shown in Fig. 8. The glucose decay curve in Fig. 8 was back-extrapolated to yield the distribution volume of 27 dl and, from the slope of the curve, the elimination rate constant of glucose was calculated to be 0.024 min$^{-1}$. Deconvolution techniques$^{22,23}$ were applied to construct the absorption profile of glucose after ingestion of dog-food under the assumption that the distribution volume and the rate constant of glucose elimination remained essentially unchanged. The posthepatic glucose delivery rates were estimated based on the blood glucose levels above the ini-

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**FIG. 7.** Time Profile of the Blood Glucose Concentration Following Ingestion of 150 g of Dog-Food during Basal Insulin Subcutaneous Infusion in a Depacreatized Dog

**FIG. 8.** Semilogarithmic Plots of the Blood Glucose Concentration above the Initial Level after an Intravenous Bolus Injection of 5 g of Glucose during Basal Subcutaneous Insulin Infusion in a Depacreatized Dog

The solid line represents the regression line of the experimental data.
tial level after the ingestion of dog-food as shown in Fig. 9. The total amount of glucose delivered to the periphery was then calculated and was about 105 g.

Under the condition of the inflow of exogeneous glucose, the blood glucose may be held at a certain constant level as long as appropriate serum insulin levels are maintained. Thus, the inflow rate of exogeneous glucose \( J(t) \) is added to the right hand side of Eq. 5 and the glucose elimination rate is set to zero:

\[
\frac{dg}{dt} = -\alpha \cdot (g_s - g') - \beta \cdot i(t) + J(t) = 0
\]...

(12)

where \( i(t) \) and \( J(t) \) are the insulin concentration and the inflow rate of exogeneous glucose at time \( t \), respectively, and \( g' \) is the desired glucose level after the ingestion of food. Rearranging Eq. 12 to solve for \( i(t) \),

\[
i(t) = \frac{J(t)}{\beta} + \frac{\alpha}{\beta} (g_s - g')
\]...

(13)

Since the \( \alpha \cdot (g_s - g')/\beta \) means the basal serum insulin concentration (refer to Eq. 11), the postprandial insulin concentration above the basal level vs. time profile required to hold blood glucose at the constant level is calculated from the following equation:

\[
i(t) = \frac{J(t)}{\beta}
\]...

(14)

The time profile of the serum insulin concentration above the basal level after the ingestion of dog-food was calculated using \( \beta \) values of 0.064—0.084 mg/µU/min/10² (see Table 1) as shown in Fig. 10. The subcutaneous insulin infu-

![FIG. 9. Time Course of the Blood Glucose Concentration Profile above the Initial Level Following Ingestion of 150 g of Dog-Food (Upper Panel) and Calculated Posthepatic Glucose Delivery Rates (Lower Panel)](image)

![FIG. 10. Time Profile of the Serum Insulin Concentration above the Basal Level Required to Hold the Postprandial Blood Glucose at a Certain Constant Level](image)

The shaded area is the range of values for the serum insulin concentration obtained by using \( \beta \) values of 0.064—0.084 mg/µU/min/10².)
sion program required to reconstruct the insulin pattern was then determined by our method. Total amounts of insulin required for the ingestion of 150 g of dog-food were calculated to be between 17.2 ($\beta=0.084$) and 22.6 ($\beta=0.064$) units. The calculated amounts of insulin were, however, extremely large judging from the data obtained from the experiment of long-term basal insulin infusion. That is, after the ingestion of 200 g of dog-food, the blood glucose levels were maintained below 300 mg/dl by a preprandial dose of 5 units of insulin.

Katz et al. have shown that about 71% of the ingested glucose was taken up by the peripheral tissue. The carbohydrate content of the dog-food used in this study was 60% and the total amount of glucose delivered to the periphery was estimated to be about 64 g at the most when 150 g of the dog-food was ingested. However, the employed deconvolution technique yielded about 105 g of glucose delivered to the periphery. In the calculation of posthepatic glucose delivery rate, it was assumed that the insulin-independent glucose elimination rate constant was independent of changes in the glucose concentration. If an increase in the glucose concentration is in fact associated with a progressive decrease in the insulin-independent glucose elimination rate constant, the employed method for constructing the absorption profile of glucose must be inadequate in terms of appropriate estimation of glucose delivery rate. In the intravenous glucose injection study, the glucose levels ranged from 41 to 179 mg/dl. On the other hand, in the single bolus subcutaneous insulin injection experiments, the average blood glucose levels ranged from 259 to 385 mg/dl. Then, the estimated value for the insulin-independent glucose elimination rate constant after the intravenous glucose injection ($\alpha=0.024$ min$^{-1}$) became five times greater than that after the single bolus subcutaneous insulin injections ($\alpha=0.0046$ min$^{-1}$). These results indicated that the insulin-independent glucose elimination rate constant varied depending on the glucose concentration and a single parameter value for $\alpha$ could not be used when blood glucose concentrations differ considerably from one test to another.

We then tentatively used half-values of the calculated postprandial serum insulin levels (based on $\beta=0.084$) and determined the subcu-

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**FIG. 11. Time Course of the Blood Glucose and Serum Insulin Levels by Prandial Insulin Subcutaneous Infusion in a Pancreatized Dog**

*Key:* (□), predetermined pattern of insulin concentration; (■), measured serum insulin concentration; (◯), measured blood glucose concentration; (○), predicted blood glucose concentration based on the Bolie model (β = 0.084 mg/µU/min/10²), bars denote subcutaneous insulin infusion rates.
taneous insulin infusion program. When a total amount of 8.6 units was infused over a period of 8 h at variable infusion rates to reconstruct the desired serum insulin pattern, the measured insulin concentration did not differ greatly from the pre-determined levels (Fig. 11). The blood glucose was maintained at relatively constant levels (59—83 mg/dl) until 14:00 in spite of the ingestion of 150 g of dog-food at 9:00. However, the blood glucose levels were lowered to less than 20 mg/dl toward the end of the insulin infusion period (later than 15:00). When the time profile of blood glucose concentrations was calculated using the Bolie model (\( \beta = 0.084 \)) on the basis of the measured insulin concentrations and estimated posthepatic glucose delivery rates, the pattern of predicted glucose levels was very different from that of the measured levels as shown in Fig. 11. The calculated glucose concentrations rose to more than 200 mg/dl between 10:30 and 13:30, the peak level being 288 mg/dl at 11:45. From these results, it became apparent that the Bolie model did not adequately provide the serum insulin concentration—time profile required to keep the postprandial blood glucose within a physiological range.

In conclusion, the Bolie model could predict the relationship between the blood glucose and serum insulin concentrations only when the blood glucose concentrations were within lower ranges as in the overnight fasted state during the basal continuous subcutaneous insulin infusion. However, it was very likely that changes in the blood glucose concentration affected the insulin-independent glucose elimination rate constant. This posed a difficulty in the use of the Bolie model in determining the serum insulin concentration—time profile required to maintain the postprandial blood glucose levels within a physiological range. The Bolie model may therefore be used to estimate the basal insulin infusion rate, but it will be necessary to develop a more appropriate method for determining the postprandial subcutaneous insulin infusion rates in the CSII system.

REFERENCES


