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Short Communication

Pharmacokinetic studies of the hypoglycemic effects of insulin in the treatment of diabetic ketoacidosis

W.A. COLBURN, W.L. HAYTON * and M. GIBALDI **

*School of Pharmacy, State University of New York at Buffalo, Amherst, N.Y. 14260 and * College of Pharmacy, Washington State University, Pullman, Wash. 99163 (U.S.A.)*

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SUMMARY

A recently developed pharmacokinetic model of the insulin-glucose system has been used to investigate the contribution of insulin-induced suppression of endogenous glucose production (EGP) to the hypoglycemic effect of insulin in the treatment of diabetic ketoacidosis and to determine the influence of the initial degree of hyperglycemia on the course of insulin treatment. Simulations of the time course of glucose concentration in the plasma following low-dose insulin therapy indicate that the hypoglycemic action of insulin is largely due to insulin-dependent glucose utilization and that suppression of EGP, if it occurs at all, contributes little to the overall effect. Nevertheless, a particularly useful characteristic of the pharmacokinetic model of the insulin-glucose system that assumes little or no suppression of EGP is its ability to predict glucose rebound when insulin has been effectively depleted. Other simulations reveal that the initial degree of hyperglycemia has little influence on the clinical outcome of low-dose insulin treatment of diabetic ketoacidosis. According to the simulation, 0.1 (U/kg)/hr intravenous infusion of insulin will produce satisfactory control of plasma glucose concentrations within 5–8 hr, assuming initial glucose concentrations ranging from 500 to 1500 mg/dl.

A pharmacokinetic model of the insulin-glucose system (Fig. 1) has been used to examine the effectiveness of insulin administered by different routes and regimens for diabetic ketoacidosis (Hayton and Grisafe, 1976). Although the model undoubtedly oversimplifies a very complex situation, it does incorporate certain critical characteristics of the insulin-glucose system including a capacity-limited insulin-independent glucose utilization process (compartment 6) and a second order insulin-dependent glucose utilization process (compartment 9) that is a function of the amount of glucose in compartment

** To whom correspondence should be addressed at: School of Pharmacy, Department of Pharmaceutics, State University of New York at Buffalo, Amherst, N.Y. 14260, U.S.A.

9 and the amount of insulin in compartment 3 (Insel et al., 1975).

An additional aspect which is implicitly incorporated in the model but which is quite controversial is the assumption that the hypoglycemic effect of insulin is due not only to an accelerated removal, but also to a lowered production rate of glucose. Basal endogenous glucose production (EGP) averages 140 mg/min in healthy volunteers (Insel et al., 1975). Similar or higher values have been observed in diabetics (Reichard et al., 1961; Weinhouse et al., 1963). The EGP used in the original model (Hayton and Grisafe, 1976) is 40 mg/min which is the average EGP in healthy adult subjects during insulin infusion and which represents a partial suppression of EGP to about one-third basal levels (Insel et al., 1975). However, whether or not insulin suppresses glucose production in the diabetic is uncertain and has been debated (de Bodo et al., 1959; Levine and Fritz, 1956; Martin and Pearson, 1971; Reichard et al., 1960; Weinhouse et al., 1963). It is of interest to determine the effects of this assumption on the predicted glucose response to insulin.

Another question that requires investigation is the influence of the initial degree of hyperglycemia on the patient's response to insulin. Hayton and Grisafe (1976) examined the effect of different insulin regimens in a simulated patient with an initial plasma glucose concentration of 1000 mg/dl. However, patients with diabetic ketoacidosis present with glucose levels ranging from 300 to 2000 mg/dl (Jaspan, 1975; Martin and Martin, 1976). Whether or not these differences are of clinical consequences in terms of the dose of insulin required to attain euglycemia or in terms of the risk of hypoglycemia are of interest but not known.

The present report addresses both questions by using modifications of the previously reported pharmacokinetic model to simulate glucose concentrations after insulin administration. The results suggest that suppression of endogenous glucose production by insulin is of little consequence to the clinical outcome of low-dose insulin treatment of diabetic ketoacidosis and that the initial degree of hyperglycemia should have little influence on low-dose insulin therapy.

Pharmacokinetic model

A detailed discussion of the pharmacokinetic model (Fig. 1) has been presented by Hayton and Grisafe (1976). Glucose concentrations in compartment 6 are analogous to plasma glucose concentrations. Endogenous production of insulin is considered negligible. The insulin-independent glucose utilization rate, V, in mg/min is

$$V = (80.8\ G_6)/(2000 + G_6) \tag{1}$$

where G_6 is the amount of glucose in compartment 6. The insulin-dependent glucose utilization rate in compartment 9 is directly proportional to the amount of glucose in compartment 9 (G_9) and to the amount of insulin in compartment 3 (I_3). The rate constant for the insulin-dependent utilization of glucose, L_{09}, in min^{-1} is

$$L_{09} = 2.5 \times 10^{-5}\ (I_3) \tag{2}$$

The contribution of lowered glucose production to the hypoglycemic effect of insulin was determined by comparing the results of simulations based on an endogenous glucose

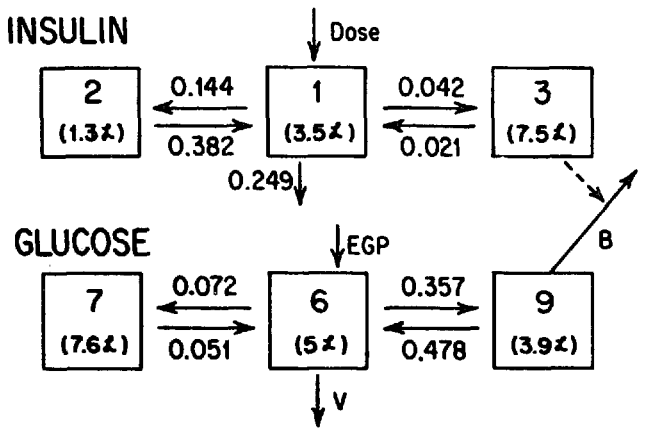

Fig. 1. Pharmacokinetic model of the insulin-glucose system. Rate constants in reciprocal minutes are shown next to arrows representing first-order transfer between compartments and insulin elimination from compartment 1. Parenthetic values are compartmental volumes in a 79 kg man. The arrow into compartment 1 represents insulin administration; the arrow into compartment 6 represents constant-rate endogenous glucose production. The arrow from compartment 6 (V) represents the capacity-limited insulin independent utilization of glucose (Eqn. 1). The arrow from compartment 9 (B) represents insulin-dependent glucose utilization the rate of which is a function of glucose concentration in 9 as well as of insulin concentration in compartment 3. In the absence of insulin, the rate of process B is zero. The stippled arrow from compartment 3 to process B denotes the insulin dependence of the process but also indicates a non-destructive pathway; insulin is not transported or cleared by this route.

production rate of either 140 mg/min (no suppression) or 40 mg/min (partial suppression).

To simulate diabetic ketoacidosis, the amount of insulin in the model was set initially at zero and a sufficient amount of glucose was added to the system to attain initial concentrations of 500, 1000 or 1500 mg/dl. To simulate insulin therapy, insulin was infused into compartment 1 at a constant rate of 0.1 (U/kg)/hr.

Numerical solutions of the differential equations describing the pharmacokinetic model were obtained using the digital computer program NONLIN (Metzler, 1969).

Results and discussion

One would expect that a dual mechanism for the hypoglycemic effect of insulin involving enhanced utilization of glucose as well as suppression of EGP would result in a more rapid decline of elevated glucose levels than that produced if insulin had no suppressive effect on EGP but only affected utilization rate. The results of simulations of the hypoglycemic effects of a continuous 0.1 (U/kg)/hr constant rate intravenous infusion of insulin (Fig. 2) indicate that this is the case. However, the results also suggest that the difference between these two models of insulin effects is unlikely to be of clinical significance. Assuming an initial glucose concentration of 1000 mg/dl, one obtains a satisfactory concentration of plasma glucose (i.e. 200 mg/dl) in about 7 hr if no suppression is assumed and in about 5 hr after initiating the infusion if partial suppression is postulated (Fig. 2). Both estimates are well within the reported range of times required to control

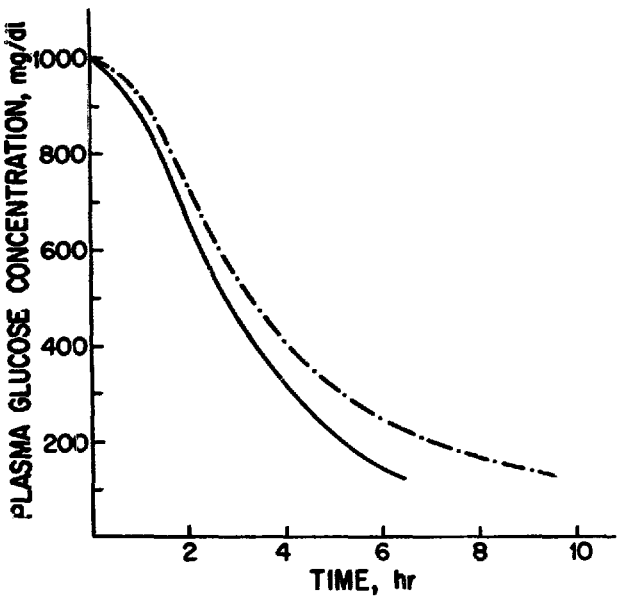

Fig. 2. Time course of plasma glucose concentration following insulin administration by a constant-rate low-dose intravenous infusion, 0.1 (U/kg)/hr, as predicted by a pharmacokinetic model that assumes partial suppression of EGP (———) or one that assumes no suppression of EGP (– · –).

blood sugar in patients with diabetic ketoacidosis using low dose insulin infusions (Martin and Martin, 1976; Soler et al., 1975).

A characteristic that differentiates the two pharmacokinetic models is the ability of the one that assumes no suppression of EGP to predict glucose rebound when insulin concentrations in compartment 3 are nearly depleted. At this time, glucose concentration in the plasma increases continuously unless additional insulin is given. Glucose rebound because of inadvertent lapses during insulin treatment of diabetic ketoacidosis is well known (Martin and Martin, 1976; Soler et al., 1975). On the other hand, the pharmacokinetic model based on partial suppression of EGP predicts a continual decrease in plasma glucose to a level of 40 mg/dl irrespective of insulin dose. This apparent defect of the model can be corrected by incorporating a feedback mechanism that relates EGP to the concentration of insulin in one of the insulin compartments.

An interesting and unexpected finding of this investigation is the prediction of a very limited dependence of clinical outcome of insulin treatment on the initial degree of hyperglycemia. Treatment with a continuous low-dose intravenous infusion of insulin is predicted to result in satisfactory control of blood glucose (i.e. to a level of 200 mg/dl) in about 4.5 hr in a patient with an initial glucose concentration of 500 mg/dl and in about 8 hr in a patient with an initial glucose concentration of 1500 mg/dl (Fig. 3). Although the initial degree of hyperglycemia differs by a factor of three, the amount of insulin required to obtain adequate control differs less than two-fold.

In conclusion, the role of insulin in suppressing endogenous glucose production is still unresolved but the results of this study help to put the question in perspective. Whether the hypoglycemic effects of insulin are due to enhanced glucose utilization alone or to

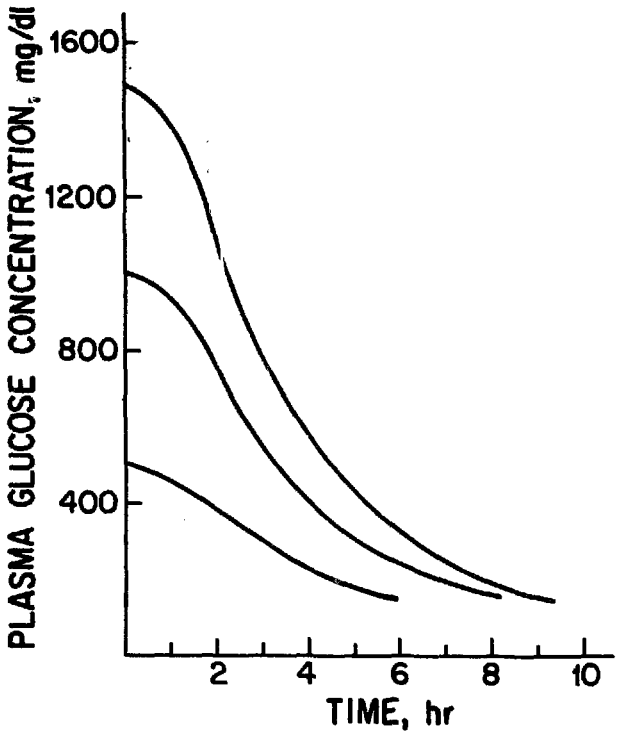

Fig. 3. Time course of plasma glucose concentration following insulin administration by a constant-rate low-dose intravenous infusion, 0.1 (U/kg)/hr, to patients with initial glucose levels of 500, 1000 or 1500 mg/dl using a pharmacokinetic model that assumes no suppression of EGP (EGP = 140 mg/min).

both enhanced utilization and reduced production is apparently of little clinical consequence. The contribution of EGP suppression, if any, to the hypoglycemic effect is likely to be small. Of greater clinical interest is the finding that the initial degree of hyperglycemia appears to be of little consequence in low-dose insulin treatment of diabetic ketoacidosis.

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