Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus

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Summary

An important defect in insulin-dependent diabetes mellitus (IDDM) is that the liver does not meet its full fuel-processing function, because many of the enzymes involved depend on high insulin concentrations in the portal vein. We tried to reactivate the liver by long-term treatment of IDDM patients with intravenous insulin in pulses, with the aim of achieving high portal-vein concentrations during and after a glucose meal.

We studied 20 IDDM patients with brittle disease; despite use of a four-injection regimen with manipulation of insulin doses, diet, and physical activity, and frequent clinic visits for at least a year, these patients still had wide swings in blood glucose and frequent hypoglycaemic reactions. The intermittent therapy consisted of 7–10 pulses of intravenous insulin, infused while the patient was ingesting carbohydrate, primarily glucose, during the first hour of a 3 h treatment; three treatments were given in a day. After 2 consecutive days' treatment, patients were treated for 1 day per week. No patient was withdrawn from the study. At the time of this analysis the duration of intermittent treatment ranged from 7 to 71 months (mean 41 [SE 5] months). Haemoglobin A_1C concentrations declined from 8·5 (0·4)% at the end of the stabilisation phase to 7·0 (0·2)% at the analysis point ($p = 0·0003$). During the same time the frequencies of major and minor hypoglycaemic events also fell significantly (major 3·0 [1·1] to 0·1 [0], minor 13·0 [2·6] to 2·4 [0·8] per month; both $p < 0·0001$).

Because the use of saline rather than insulin pulses would have led to unacceptable hyperglycaemia we opted for a historical control design. The absence of a true control group limits the interpretation of these preliminary results, but we believe further studies of hepatic and muscle metabolism before and after long-term intermittent intravenous insulin therapy would be worth while.

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Introduction

During the past 30 years, study of diabetic tissues has shown major biochemical defects in fat, muscle, and liver. Nevertheless, no new therapy has emerged that directly addresses these defects. About 17 years ago, our laboratory initiated studies[1-5] to find out why conventional insulin therapy, including insulin pumps, fails to regulate circulating blood glucose concentrations and does not prevent progress of complications of insulin-dependent diabetes mellitus (IDDM). We chose an organ-focused approach, and our attention was quickly drawn to the pivotal fuel-processing role of the liver in normal subjects but not in insulin-treated diabetic patients.

When a healthy person ingests a glucose meal, the glucose is collected by capillaries surrounding the stomach and small intestine, which drain into the portal vein. The beta cells of the pancreas, stimulated by the increasing portal glucose concentrations, secrete insulin into the vein. The portal vein divides into sinusoids, which ensure close contact between portal venous blood and hepatocytes. The bimolecular signal of very high insulin and glucose concentrations stimulates the synthesis or maintains the activity of insulin-dependent fuel-processing enzymes such as glucokinase, phosphofructokinase, and pyruvate kinase.[6-12] By means of these enzymes and associated biochemical pathways, the liver can autoregulate circulating blood glucose—ie, take up glucose during meals and release it during sleep or fasting.

50% of the insulin secreted by the pancreas during a meal is removed by the liver on first pass.[13] Thus, the liver is the principal metabolic target organ of both the gastrointestinal tract and the endocrine pancreas in normal subjects. By contrast, in IDDM patients after, say, 10 units of regular insulin subcutaneously, the highest free insulin concentrations are achieved in the systemic circulation rather than the portal vein and are about 30–40 μU mL; portal venous insulin concentrations are similar or smaller, compared with portal values of 200–500 μU mL in normal subjects.[14] If the liver needs concentrations of this order to maintain the activity of its fuel-processing enzymes, the liver of an IDDM patient on a conventional insulin regimen could never function normally.

We reasoned that if the liver of an IDDM patient could be perfused with near-normal concentrations of insulin during meals, the organ could be reactivated. Studies with the artificial pancreas produced by Miles Laboratory (Elkhart, Indiana, USA) showed that, with increases in the respiratory quotient and carbohydrate oxidation rates as indices of adequate hepatic insulin exposure, the metabolic integrity of the liver of the IDDM patient could be re-established.[1,3,5] However, the very labour-intensive artificial pancreas took about 72 h to accomplish this task.

We then tried to develop an insulin algorithm that would activate the liver of such patients more rapidly and to see whether it had any clinical value.

In this preliminary study, such an insulin algorithm was used. Insulin was administered as a series of pulses rather than as a square wave.[16] Pulses should have greater potential for hepatic activation than a continuous infusion of insulin since it is possible to manipulate the rate at which insulin concentrations change, the magnitude of each pulse, and the duration of insulin exposure, and to superimpose the pulses on a rising baseline, any or all of which may be metabolically important signals. We postulated that if hepatic activation was achieved and maintained in patients with "brittle" IDDM by this process, concentrations of haemoglobin A_1C (HbA_1C; an indicator of blood glucose control) and the frequency of hypoglycaemic reactions should decrease.

Patients and methods

Twenty insulin-dependent (C-peptide-free) diabetic patients (fifteen female, five male) who had wide swings in fingerstick blood glucose concentrations, very frequent hypoglycaemic reactions, or both, were invited to take part in this study, which was reviewed and approved by the University of California, Davis, institutional review board. All patients gave written informed consent. The mean age of the patients at the start of long-term intermittent intravenous insulin treatment was 46 (SE 4, range 5–78) years, duration of diabetes 25 (3, 2–54) years, and body weight 63 (3, 19–96) kg. Most of the patients had one or more complications of diabetes including nephropathy, retinopathy, and neuropathy. The mean HbA_1C proportion on entry was 8·5 (SE 0·4)%, and the average daily insulin dose was 34 (3) units. No subject was withdrawn from the study. At the time of this analysis the duration of long-term intermittent intravenous insulin therapy ranged from 7 months in the newest recruit to 71 months in the oldest (mean 41 [SE 5] months).

Major unpredictable hypoglycaemic reactions were defined as those of such severity that the patient could not independently resolve or treat the hypoglycaemia and required outside help. Minor hypoglycaemic reactions were defined as low blood glucose concentrations associated with some non-incapacitating symptoms including hunger, sweating, and tachycardia. Information on these reactions was obtained before, during, and at the end of the study; where possible we questioned a relative of the patient, since questioning of the patient can lead to falsely low reporting of hypoglycaemic reactions (especially severe ones). The subjects reported 3·0 (1·1) major reactions per month and 13·0 (2·6) minor reactions per month for the year before the intermittent intravenous insulin phase of the study.

We used a McGaw-Accu Pro Infusion Pump (Carrolton, Texas, USA) controlled by an Epson Geneva PX-8 Laptop computer, or a Bionica MD-110 infusion pump (Los Angeles, California, USA). Insulin was infused through a 22 gauge cannula into a hand or forearm vein. 7–10 intravenous pulses (about 2 units of insulin per pulse) were infused over 60 min while the patient ingested 40–100 g glucose, together with, in some cases, high glycaemic index foods (crackers or bread)[17,18] to improve palatability. Blood glucose was measured by fingerstick before and every 30 min throughout the procedure. More glucose was given as needed every 30 min, and at the start of each 3 h period to maintain blood glucose at 8·33–13·9 mmol/L at all times. The insulin pulses were given during the first hour of a 3 h treatment and three treatments were given each treatment day. We aimed for peak post-pulse free insulin concentrations of at least 200 μU mL; concentrations were confirmed by radioimmunoassay with immediate processing of equal volumes of serum and 25% polyethylene glycol to separate free from bound insulin in peripheral venous blood. Initial therapy consisted of 2 treatment days, than treatment was given on 1 day per week.

Respiratory quotient measurements with a Metabolic Measurement Cart (Sensormedics, Anaheim, California, USA) were obtained[13] before and every 60 min throughout the study period. An increase in the respiratory quotient to more than 0·90 was used as the index of therapeutic efficacy. If this increase was not achieved by 3–4 h after initiation of intravenous insulin therapy, larger pulses were administered until the respiratory quotient exceeded 0·90 on that and subsequent occasions.

At least 1, or in most cases 2, years before entry to the study, all participants, who were selected because of their brittle diabetes, were put on a four-insulin-injection regimen with careful attention paid to diet and exercise. The objectives of this phase of the study were to achieve reductions in both mild and severe unpredictable hypoglycaemic reactions and HbA_1C percentage. In most cases, these objectives were achieved to a limited extent. The participants were maintained on the four-injection regimen and seen monthly throughout the study period at the University of California Davis, Medical Center Diabetes Clinic. Between clinic visits, the patients maintained close telephone contact (once or twice a week) with the faculty, and appropriate adjustments in insulin, diet, and activity were made. They continued to measure and record blood glucose concentrations by fingerstick 3–4 times daily with the aim of maintaining blood glucose concentrations between 5·55 and 11·1 mmol/L. Blood samples for HbA_1C measurement were taken every 2 months. This system was implemented for at least a year before and throughout the study period.

HbA_1C was measured on a Varian Vista 5500 HPLC system equipped with a Waters SP-5PW column. To check the accuracy and reproducibility of the system, haemolysates from 19 patients were sent to the Joslin Diabetes Center to be tested by the Diabetes Control and Complications Trial HbA_1C reference laboratory. The values did not differ significantly from those in our laboratory (7·6 [SE 1·4] *vs* 7·4 [1·5]%). The range in non-diabetic subjects is 4·0–6·0%. The coefficients of variation were 5·9% within assays and 6·8% between assays.

The ideal control group would receive saline rather than insulin pulses but would otherwise be treated in exactly the same way as the group receiving insulin pulses. However, such control patients would quickly become very hyperglycaemic, since large amounts of glucose must also be ingested. We therefore judged such a design unethical. Since this was a preliminary study, we used a historical control design, with each patient serving as his or her own control, though we are well aware that the absence of a true control group makes cautious interpretation of our results essential. HbA_1C results were analysed every 6 months, approximately. The method of least squares was used to approximate the rate of change in HbA_1C values, and the slope for each subject was taken as his or her response. The Wilcoxon signed rank test was then used to test whether the mean slope differed from zero. The Wilcoxon matched pairs test was used to assess the difference in the frequencies of hypoglycaemic reactions before and after long-term intermittent intravenous insulin therapy.

Results

HbA_1C values declined from 8·5 (SE 0·4)% at entry to 7·0 (0·2)% at the time of this analysis, when the length of time on therapy ranged from 7 to 71 months among the subjects (figure). The method of least squares was used to approximate the rate of change in HbA_1C of each subject; 18 of the 20 subjects showed a decline in the HbA_1C with time, which in 17 cases was apparently linear (for the other 3 patients we had too few data to assess linearity reliably). With the Wilcoxon signed rank test (used because the slopes were not normally distributed) the mean slope differed significantly from zero ($p < 0·0003$). Time series analysis revealed no significant trends, perhaps because of the small number of observations (average 7) per participant. There was no significant change in body weight whether or not the 2 children were included in the analysis.

The subjects reported a decrease in the frequency of hypoglycaemic reactions, which became apparent after 3–4 months of pulse therapy. The subjects had 3·0 (2·6) major

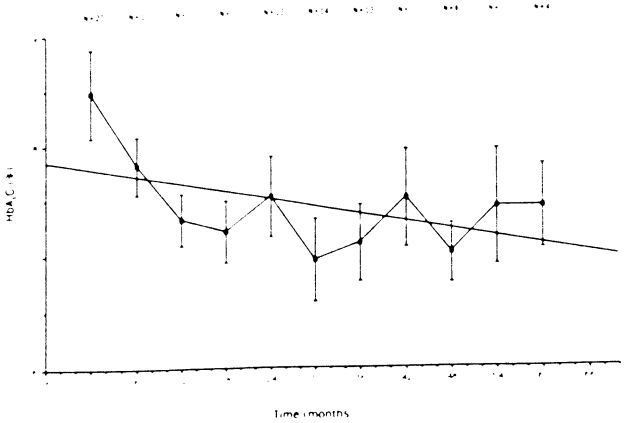

Figure: **Least squares analysis of HbA_1C values (mean and SE)**

and 13·0 (2·6) minor hypoglycaemic reactions per month during the year preceding the activation phase. However, after a mean 41 (5) months in the activation phase, the frequencies of major and minor hypoglycaemic reactions declined to 0·1 (0) and 2·4 (0·8) per month, respectively (both $p < 0·0001$, Wilcoxon matched pairs test).

Discussion

For the past 70 years, the primary goal of insulin therapy in IDDM has been to maintain circulating blood glucose concentration within the normal range. The number of deaths from diabetic ketoacidosis has fallen greatly with this therapeutic aim. However, even with good to excellent blood glucose control, complications such as retinopathy, nephropathy, and neuropathy develop.

We postulated that the low insulin exposure of the liver of IDDM patients would reduce the activity of insulin-dependent glucose-processing enzymes, such as glucokinase and phosphofructokinase. We have tried to re-establish the ability of the liver to autoregulate blood glucose concentrations through these enzymes by providing the bimolecular insulin and food signal on a regular basis to the liver of IDDM patients. We emphasise that this study is based on inferences from a large body of biochemical and physiological evidence, mainly from animal studies. Studies in human beings on glucokinase, for example, such as those in rats,[9,10] are needed to provide the detailed biochemical basis for our hypothesis. However, it is difficult to take many liver biopsy samples from either a healthy person or a patient with IDDM. We have therefore used an increase in the respiratory quotient to 0·90 or greater as the primary index of re-established metabolic integrity of the liver in the diabetic participants. With this index, we found that the liver could be activated more quickly (6–9 h) with the McGaw/Epson unit delivering insulin pulses than with the artificial pancreas used for continuous glucose-controlled insulin infusion (48–72) h.

Our previous approach (2 days [6 treatments] of pulsatile insulin therapy) did not improve glucose tolerance in well-controlled IDDM patients.[16] The reasons for this failure are probably related to the pronounced increase in muscle glycogen stores during the insulin exposure and the short (4 days) duration of the study. The administration of a glucose meal to diabetic patients whose muscle glycogen stores are already maximally expanded, as expected, resulted in impaired glucose tolerance.

We can still only guess why the protocol used in this study was so effective in lowering HbA_1C proportions and decreasing the frequency of hypoglycaemic reactions. Non-diabetic individuals stimulate hepatic processes, by way of high portal-vein concentrations of insulin and glucose, every time they eat a meal. The study patients' livers were stimulated three times during 1 day of the week rather than three times every day as in healthy people. The reason for the success may lie in the long half-life of glucokinase; the half-life of rat glucokinase is 3–4 days[10] and that of the human enzyme may be longer because the human metabolic rate is lower. Another explanation, which we consider less likely, is that the participants were seen briefly each week by a physician, and that the increased attention contributed to the improvement.

Use of saline pulses instead of insulin pulses would have allowed us to assess unequivocally the effectiveness of long-term intravenous insulin therapy but, as we have said, this design would have been unethical. Nevertheless, the absence of a control group requires that the data presented here be interpreted cautiously.

The procedure we have used is standard intravenous insulin therapy given on a regular basis. The procedure entails the intravenous infusion of insulin in pulses, into a hand or forearm vein with appropriate glucose ingestion to prevent hypoglycaemia. The goals of standard intravenous insulin therapy and long-term intermittent intravenous insulin therapy are identical—ie, improved blood glucose control. We have observed no adverse side-effects of this procedure in more than 60 person-years of use.

This approach led to improvements in blood glucose control in patients with brittle diabetes without any change in daily insulin requirements. We interpret these data as showing that long-term intermittent intravenous insulin therapy for IDDM is associated with improved hepatic autoregulation of circulating blood glucose concentrations and seems a safe and effective treatment of patients whose diabetes is difficult to control. However, the absence of a true control group means that more focused controlled studies on hepatic and muscle metabolism, before and after long-term intermittent intravenous insulin therapy, are needed to confirm our interpretation.

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