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Comparison of Continuous and Intermittent Intravenous Insulin Therapies for Diabetic Ketoacidosis*

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Summary. Twenty-six diabetic ketoacidotic patients were treated with 3 different intravenous insulin regimes. Group (A) received 50 U initially and at 2 h intervals. Groups (B) and (C) were given continuous infusions of 10 and 2 U per hour respectively without added albumin. In addition, Group (C) received a loading dose of 3 U. The dosages were reduced when serum glucose declined to 300 mg/100 ml. Criteria for admission to the study included a plasma glucose above 350 mg/100 ml, plasma bicarbonate less than 9 mmol/l, serum ketone-bodies detectable by nitroprusside test at 8-fold or greater dilution, and arterial pH less than 7.3. The rate of normalization of blood glucose, bicarbonate, ketone bodies, and pH did not differ between Group (A) and (B). In contrast, the changes in pH, glucose, and ketone-bodies were significantly slower in Group (C). Two patients of Group (C) had worsening of these biochemical parameters during the first 6 h. They were treated successfully with regimen A. At 2 h, plasma immunoreactive insulin concentrations were 47 ± 15, 135 ± 19, and 25 ± 3 μU/ml in previously untreated patients in Groups (A), (B) and (C), respectively. Potassium requirements to maintain adequate blood levels were significantly higher in Group (A). The data demonstrate that 10 U/h infusion of insulin is as effective as 50 U administered intravenously every 2 h. The amount of insulin infused should be reduced to 5 U/h when plasma glucose has declined to 300 mg/100 ml. The recovery is slow, plasma insulin concentration is inadequate and treatment failure may occur with very low insulin doses (2 U/h).

Key words: Diabetic coma, ketoacidosis, intravenous insulin-infusion, ketone-bodies.

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Traditionally, large doses of insulin in the range of hundreds of units have been advocated [1–4] in the treatment of diabetic ketoacidosis. However, there had been some scepticism over both the necessity for such high doses and the existence of insulin resistance in ketoacidosis that such high doses implied [5, 6]. This scepticism has recently been revived, as emphasized by Sönksen et al. [7], who found rapid biochemical and clinical improvement in severe diabetic ketoacidosis with insulin infusion rates between 1.5 and 12 U/hour. Alberti et al. [8], showed that relatively small doses of insulin (average 16 U initially and 5 to 10 U hourly) were effective in the treatment of severe diabetic ketoacidosis when given by the intramuscular route.

There have been several reports utilizing low doses of insulin (1.2 to 12 U/hour, with or without an initial priming dose of 0.5–12 U) by the intravenous route [9, 10, 11]. All groups found their regimes effective in the treatment of ketoacidosis. This literature, however, met with unfavourable criticism [12] primarily because of the lack of a well-defined control group for comparison. Also, the degree of ketoacidosis was minimal in many of the reported cases.

Most recently, Kitabchi et al. [13] studied the efficacy of low-dose (initial 0.1 U per lb. body weight, followed with 5 U/hour) intramuscular insulin therapy. This regime was as effective as a more traditional one. The present study was designed to compare the efficacy of 2 and 10 U/hour *intravenous* insulin infusions with a conventional treatment, 50 U of insulin administered intravenously at 2 hour intervals. Diagnostic criteria of diabetic ketoacidosis were well-defined. Measurement of plasma ketone bodies was included as an indication of resolution of ketoacidosis.

Methods

Patients: Twenty-six patients with diabetic ketoacidosis were studied at the Los Angeles County-University of Southern California Medical Centre. Their ages were 37 ± 3 (SEM) years (range 17 to 79). Eight patients were newly diagnosed diabetics without prior insulin therapy, 16 were insulin-dependent diabetics, and 2 cases had been previously controlled by diet and sulphonylurea drugs.

Patients included in this study met the following criteria: plasma glucose above 350 mg/100 ml; plasma bicarbonate below 9 mmol/l; pH less than 7.3, serum ketone-bodies positive with nitroprusside test in 8-fold or greater dilution, and ketones present in the urine; no insulin therapy during the preceding 24 h (this criterion was included to avoid superimposition of therapy on recently administered insulin); no clinical evidence of acute myocardial infarction, congestive heart failure, shock or severe infection.

Insulin Therapy: Patients were randomly assigned to one of the 3 insulin regimes. Group (A) intermittent bolus group was comprised of 10 patients who received 50 U regular (crystalline Zinc) insulin intravenously at the beginning, and at 2 hourly intervals. The insulin dose was reduced to 25 U when plasma glucose became 300 mg/100 ml. Group (B) and (C) were given continuous intravenous infusions of insulin at 10 U/hour (9 cases), and 2 U/hour (7 cases), respectively. Insulin infusion rates were reduced to 5 U/hour in Group (B) when plasma glucose became 300 mg/100 ml. Group (C) patients were given an intravenous loading dose of 3 U. Regular insulin (u-100) was diluted to 2 or 4 U per ml in saline (0.154 mol/l), without adjuvant. Insulin solution was delivered by a syringe pump using a 60 ml polyethylene syringe. Insulin content on sequential aliquots over a 12-h period were measured [14] in vitro and demonstrated 83% delivery.

Fluids: Fluid therapy was uniform throughout. Saline (0.154 mol/l) was initially administered at rates sufficient to achieve a net-positive balance of 4 l over 12 h. When the plasma glucose reached 300 mg/100 ml, fluid therapy was changed to glucose (5 g/100 ml) in saline (0.154 mol/l) given at rates adequate to keep the plasma glucose above 200 mg/100 ml. Potassium as KCl was administered at 20–30 mmol/l of intravenous fluid when the serum potassium fell below 4.5 mmol/l. Sodium bicarbonate was given to only one patient who received 88 mmol to bring the pH from 6.9 to 7.1.

Monitoring: Patients were studied for a 12-hour period beginning at the time of first insulin dose. Plasma glucose, bicarbonate, electrolytes, total serum ketone-bodies (acetoacetate, and 3-hydroxybutyrate) [15] were obtained initially and every 2 hours thereafter. Plasma immunoreactive insulin (IRI) levels [14] were also obtained in those patients previously untreated with insulin. In Group (A), plasma samples for IRI were collected just prior to the next insulin dose. Glucose, electrolytes and pH were measured by the hospital laboratory. The results for each group were compared by the pooled variant-analysis method with comparison of means by the Student's t-test.

Results

Groups were well matched in terms of numbers, age, and number of newly diagnosed diabetics. All patients were in severe diabetic ketoacidosis (Table 1) although none were clinically comatose.

Glucose

The fall in plasma glucose was roughly linear in all groups (Table 1). During the initial 2 h, the plasma glucose declined by 39 ± 4 (SEM), 34 ± 4, and 23 ± 3% of the initial levels in Groups (A), (B), and (C), respectively. The changes in Groups (A) and (B) were not statistically different, both being significantly greater ($P<0.05$) than Group (C). Plasma glucose reached 300 mg/100 ml in 3.4 ± 0.4 and 4.3 ± 1.2 hours in Groups (A) and (B) (P = N. S.). In contrast, Group (C) took longer to reach this level, 7 h ($P<0.05$), with 3 patients not attaining this level by the end of the 12-h study period.

The fluid therapy was started prior to initiation of insulin therapy in 3 patients of Group (B). Plasma glucose fell by a mean of 58 mg/100 ml in 1 h with fluid therapy alone. However, the study period began with the first dose of insulin.

An inability to maintain the plasma glucose above 200 mg/100 ml by glucose (5 g/100 ml) infusion occurred in 2 patients of Group (B). It was necessary to reduce the insulin infusion rate to 5 U/hour to avoid hypoglycaemia.

Ketone-Bodies

The decline in total serum ketone-bodies (3-hydroxybutyrate plus acetoacetate) is given in Table 1 and Figure 1. Statistical analysis of the percent

Table 1. Effect of treatment on biochemical data in various groups of ketoacidotic patients studied

Time in h	0	2	4	6	12
Serum glucose mg/100 ml					
Group A	754±62	451±48	322±43	284±36	
B	635±84	441±77	331±55	297±34	
C	671±95	509±90	454±81	392±84	
Serum potassium[a] mmol/l					
Group A	4.9±0.3	3.9±0.2	4.3±0.2	4.2±0.2	4.2±0.2
B	4.9±0.4	4.5±0.2	4.3±0.1	4.2±0.2	4.2±0.3
C	5.0±0.3	4.7±0.2	4.3±0.3	4.2±0.1	4.1±0.2
Serum inorganic phosphate mg/100 ml					
Group A	5.7±0.8	2.4±0.4	1.6±0.2	1.4±0.3	0.8±0.1
B	6.6±0.7	5.2±0.7	3.1±0.6	2.4±0.3	1.7±0.3
C	4.8±0.8	3.7±0.5	3.0±0.4	2.7±0.4	2.0±0.3
Serum bicarbonate mmol/l					
Group A	5.8±0.8	7.0±1.0	10.5±1.6	12.6±2.3	17.0±2.0
B	6.2±0.7	8.5±0.8	10.8±1.0	12.1±0.8	18.4±1.7
C	7.4±1.0	9.4±1.5	10.0±2.3	10.7±1.9	14.8±2.6
Ketone-bodies[b] mmol/l					
Group A	18.5±1.0	18.0±0.9	14.1±1.1	11.3±1.3	7.3±1.5
B	16.5±1.3	13.2±1.3	12.6±1.0	9.2±1.2	5.5±0.7
C	16.4±2	15.2±2.1	14.5±2.7	13.9±2.5	10.8±2.9
Blood pH[c]					
Group A	7.14±0.04			7.28±0.05	7.36±0.03
B	7.14±0.04			7.30±0.03	7.37±0.02
C	7.19±0.04			7.26±0.05	7.28±0.04[d]

Values are Mean ± SEM
Group A received 50 U insulin intravenously every 2 h. Group B, and C were given continuous intravenous infusions of 10 and 2 U/hour respectively.
[a] Patients received intravenous infusions of KCl when serum potassium was <4.5 mmol/l. The amounts of potassium infused were 146 ± 17[d], 77 ± 11 and 80 ± 8 mmol in Groups A, B, and C respectively.
[b] Ketone-bodies (acetoacetate + 3-hydroxybutyrate)
[c] Blood pH was arterial at 0 h. Subsequent readings were mostly on venous blood samples.
[d] $P<0.05$ compared to other groups.

decline in total serum ketone bodies in 3 groups reveals that, at both 6 and 12 h, Group (C) had a slower improvement ($P<0.05$) than either Groups (A) or (B). Groups (A) and (B) were not significantly different from each other.

pH

The improvements in pH are given in Table 1. The changes in Group (C) were significantly slower ($P<0.05$) compared to other groups.

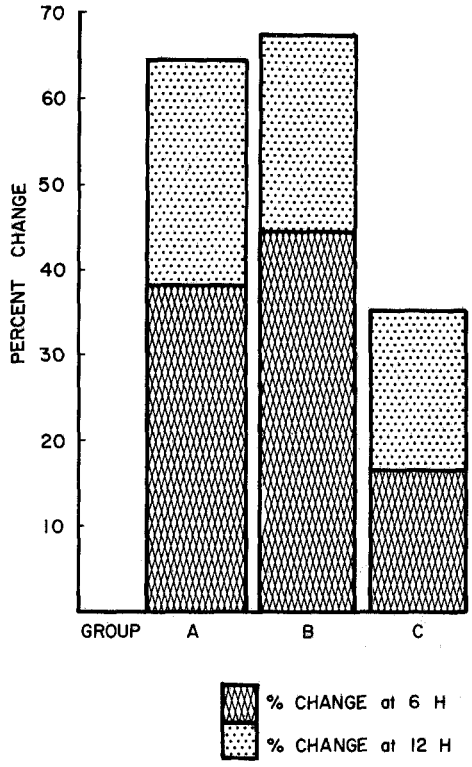

Figure 1. Percent decline in total ketone-bodies at 6 and 12 h. Changes were slower ($P < 0.05$) in Group (C) compared to Groups (A) and (B)

Bicarbonate

The changes observed in serum bicarbonate concentrations are summarized in Table 1. Group (C) had slower improvement in serum bicarbonate levels; however, this was not significant statistically. The time required to improve serum bicarbonate to 15 mmol/l was 8.9 ± 1.7 and 8.3 ± 1 h in Groups (A) and (B) respectively. In Group (C), there were 3 patients where serum bicarbonate remained less than 15 mmol/l even at 12-h.

Serum Potassium

On admission there was wide variation in serum potassium concentrations. It ranged from 3 to 6.8 mmol/l. As per protocol intravenous potassium was administered when serum potassium was <4.5 mmol/l. Several patients thus received potassium therapy in the first hour, and almost all of them were getting it by the 5th hour. The sequential changes in various groups and the amounts of potassium given are summarized in Table 1. Group (A) required more potassium replacement to maintain

adequate blood levels ($P<0.01$). Unfortunately, potassium lost in urine was not monitored.

Plasma Immunoreactive Insulin (IRI) Levels

Only patients without prior insulin therapy were studied. At 0 time, IRI was 9 ± 2 μU/ml in all groups. In Group A (3 cases), the IRI levels were 47 ± 15 μU/ml at 2 h, 66 ± 21 μU/ml at 4 h, and 54 ± 26 μU/ml at 6 h. Insulin delivered at 10 U/hour achieved steady state serum levels of 135 ± 19, 124 ± 17, and 136 ± 21 μU/ml at 2, 4 and 6 h respectively in 3 cases, and delivery at 2 U/hour achieved levels of 25 ± 3, 25 ± 4, and 23 ± 6 μU/ml at 2, 4, and 6 h respectively in 4 cases.

Failures and Complications

There were two "treatment failures" in Group (C), where plasma total ketone-bodies remained unchanged and pH and bicarbonate levels deteriorated slightly. The plasma glucose, however, declined by 30.5% of the initial value in first 2 h. Both patients were juvenile diabetics, one being a newly diagnosed man and the other an insulin-dependent woman. These patients did not differ clinically at the onset from those patients who responded more promptly. They were eventually treated with boluses of 50 U of insulin administered intravenously every 2 h. These two cases and all others had resolution of their diabetic ketoacidosis and recovered without complications or sequelae.

Discussion

Previous investigators [9, 10, 11] had reported successful treatment of diabetic ketoacidosis using infusion rates of 1.2 to 12 U/hour. However, in these studies no comparisons were made with conventional high-dose treated patients. Also, several patients did not meet the biochemical diagnostic criteria of ketoacidosis [12].

We report a controlled, randomized study which compares three intravenous insulin regimes. All patients treated with 50 U insulin every 2 h (Group A) and insulin infusion at a rate of 10 U/hour (Group B) showed relatively rapid resolution of the biochemical markers of ketoacidosis. The recovery rates in these two groups were identical. In contrast, the recovery rates were significantly slower in patients treated with 2 U/hour infusions (Group C). There were two treatment failures in this group. Recently, Clumeck et al. [16] have also reported two cases who had inadequate biochemical response to 5 U of insulin administered intravenously every hour. Therefore, very low doses of insulin (<5 U/hour) should not be used for adult patients in severe diabetic ketoacidosis.

Infusions of very small amounts of insulin, 1 [17] and 1.2 U/hour [10], have produced lowering of blood glucose in diabetic patients. Also, insulin in moderate concentration of 25 μU/ml inhibits lipolysis in isolated rat fat cells [18]. These would suggest that the IRI levels of 25 ± 3 μU/ml observed in our 2 U/hour infusion Group (C) could be considered satisfactory. However, two "treatment failures" and slower resolution of ketoacidosis in this group would indicate the inadequacy of such plasma IRI concentrations therapeutically. The nadirs of plasma IRI concentrations in Group (A), the intermittent insulin treated group, were 47 to 66 μU/ml. These were 2 to 3-fold higher than the steady state levels in Group (C). The peak IRI levels would be much higher. In Group B (10 U/hour infusion group), IRI levels were 135 ± 19 μU/ml. These would seem therapeutically desirable concentrations because these are close to the portal vein insulin levels found 7 to 17 minutes post-glucose load in man [19]. Such insulin concentrations are effective in inhibiting glycogenolysis, and in reducing gluconeogenesis in the liver [20].

Soler et al. [21] report that the small doses of insulin administered intravenously (8 U/hour infusion) or intramuscularly (10 U/hour) led to a slower recovery from ketoacidosis, when compared retrospectively with a group treated with large intravenous boluses of insulin. In fact, their groups were not significantly different, when serum bicarbonate level of <20 mmol/l was the criterion for the resolution of ketoacidosis.

We monitored plasma potassium carefully, and hypokalaemia was not a problem in any of our cases. Potassium supplements required to maintain adequate blood levels were significantly higher in Group (A) compared to others. It has been stated previously that large doses of insulin lead to faster fall of plasma potassium [11]. Our observations disagree with those of Soler et al. [21], who reported identical potassium needs in patients treated with low or high insulin doses. Unfortunately, potassium lost in the urine was not monitored and we were unable to determine the amounts of potassium retained during 12 h period in various groups.

The current study demonstrated once again that hydration alone affects plasma glucose [8]. There was a gradual and linear fall in plasma glucose in all patients, even in those who showed no change in

plasma ketone-bodies, bicarbonate and pH. This disparity between the response of plasma glucose and the response of the biochemical markers of ketoacidosis illustrates the danger of using the fall in plasma glucose alone as an indication of therapeutic success.

Continuous intravenous infusion as a therapeutic modality is currently accepted for such drugs as heparin and certain antibiotics, where constant serum levels are desirable and where prompt cessation of action of the administered drug may become medically advisable. The intravenous infusion of insulin has such advantages over intramuscular, subcutaneous and intermittent intravenous modes of insulin therapy. Evenness of delivery, absorption of full dose assured (especially pertinent in the hypotensive patient), abrupt cessation of effect upon discontinuance of delivery, lack of repeated injections for the patient, and predictable linear changes in most biochemical variables are among these advantages.

We feel that continuous intravenous insulin infusion has a place in the treatment of diabetic ketoacidosis. An infusion of 10 U/hour is effective, but the dose should be reduced to 5 U/h when plasma glucose has fallen to 300 mg/100 ml. It must be re-emphasized that any method employed must be carefully monitored and individually adjusted.

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