Treatment of Diabetic Ketoacidosis Using Normalization of Blood 3-Hydroxybutyrate Concentration as the Endpoint of Emergency Management

A randomized controlled study

M. Ivan Wiggam, MRCP
Maurice J. O'Kane, MD
Roy Harper, MD
A. Brew Atkinson, MD
David R. Hadden, MD
Elisabeth R. Trimble, MD
Patrick M. Bell, MD

OBJECTIVE — To compare the efficacy of an extended insulin regimen using correction of hyperketonemia as endpoint with a more conventional regimen in the treatment of diabetic ketoacidosis.

RESEARCH DESIGN AND METHODS — A total of 22 patients admitted to a Belfast teaching hospital with clinical and biochemical features of diabetic ketoacidosis (pH <7.25 and/or bicarbonate <16 mmol/l) were randomized to either conventional or extended insulin regimens. In the conventional regimen, insulin was administered at 5 U/h until near-normoglycemia (blood glucose ≤10 mmol/l) and then administered at a reduced rate until clinical recovery. In the extended regimen, administration of insulin at 5 U/h was continued beyond attainment of normoglycemia, until resolution of hyperketonemia (3-hydroxybutyrate <0.5 mmol/l). Main outcome measures were 3-hydroxybutyrate and bicarbonate levels during the 24 h after attainment of near-normoglycemia.

RESULTS — After near-normoglycemia, correction of hyperketonemia was achieved earlier with the extended treatment (5.9 ± 0.8 vs. 21.8 ± 3.4 h, $P = 0.0004$ [mean ± SD]). The area under the curve of 3-hydroxybutyrate against time for 24 h after near-normoglycemia was reduced with the extended treatment (24.9 ± 3.8 vs. 55.9 ± 6.7 mmol · l^{-1} · h^{-1}, $P = 0.001$). These differences remained statistically significant after adjustment for higher baseline levels of 3-hydroxybutyrate at near-normoglycemia in the extended treatment group. Bicarbonate levels at 6 and 12 h after near-normoglycemia were not significantly different between groups.

CONCLUSIONS — The extended insulin regimen, which was easy to implement at ward level, produced a more rapid resolution of ketosis than the conventional regimen.

Diabetic ketoacidosis remains a major problem of uncontrolled diabetes with significant morbidity and mortality (1–3). In the pathogenesis of ketoacidosis, relative insulin deficiency and counterregulatory hormone excess (4) lead to overproduction and underutilization of glucose resulting in hyperglycemia (5,6). Increased lipolysis leads to excessive formation of ketone bodies, which accumulate to produce a metabolic acidosis (7). Insulin therapy promotes a reversal of these metabolic derangements by suppressing hepatic production of both glucose (8) and ketones (9), in addition to increasing glucose utilization (6) and ketone body clearance (10).

From the Sir George E. Clark Metabolic Unit (M.I.W., R.H., A.B.A., D.R.H., P.M.B.) and the Department of Clinical Biochemistry (M.J.O'K., E.R.T), Royal Victoria Hospital; and the Department of Clinical Biochemistry (E.R.T.), The Queen's University of Belfast, Belfast, Northern Ireland, U.K.

Address correspondence and reprint requests to Patrick M. Bell, MD, Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast BT12 6BA, U.K.

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In the early 1970s, the dose and rate of insulin administration in diabetic ketoacidosis received much attention (11–16). Despite initial skepticism (17,18), it subsequently became established that relatively low doses of insulin administered by continuous intravenous infusion or intramuscular injection were appropriate for the vast majority of cases (19). Most modern protocols now recommend a constant rate of insulin administration (usually 5–10 U/h) until near normalization of plasma glucose (20–23).

It is recognized that ketosis and acidosis may persist for many hours after correction of hyperglycemia (16,18,24,25). There is a broad consensus that further insulin is required after normalization of blood glucose, along with intravenous dextrose to avoid hypoglycemia. Most researchers recommend that the rate of insulin be reduced during this phase, perhaps by 50% (20), or by a variable amount, depending on the blood glucose (21,22). It is usually suggested that this second phase of insulin administration should continue until the patient is eating again, and an overlap with the first subcutaneous insulin injection is advised to avoid hypoinsulinemia (20,21). Despite these recommendations, it is not uncommon for relapse of ketoacidosis to occur after correction of hyperglycemia. This may be attributed to either an inadequate rate or a premature cessation of intravenous insulin administration (6,20,25).

We have undertaken a randomized clinical study examining the efficacy of an extended insulin regimen, in which insulin is administered at a constant rate from presentation until normalization of blood 3-hydroxybutyrate concentration, and then administered at a reduced rate until oral food intake is reestablished. Use of capillary blood 3-hydroxybutyrate concentration as the primary endpoint was facilitated by hourly measurement using a bedside-reflectance meter. This new regimen is compared with a more conventional protocol in

Table 1—*Measurements at presentation with ketoacidosis*

	Conventional insulin regimen	Extended insulin regimen
n	10	12
Age (years)	22.4 ± 2.7	37.1 ± 6.2
Sex (M/F)	3/7	4/8
BMI (kg/m²)	24.6 ± 1.9	23.7 ± 0.8
HbA_{1c} (%)	10.5 ± 1.0	11.1 ± 0.8
Duration of IDDM (years)	6.5 ± 1.3	12.2 ± 3.9
Plasma glucose (mmol/l)	25.2 ± 1.5	29.7 ± 3.3
Venous blood pH	7.11 ± 0.04	7.06 ± 0.03
Blood bicarbonate (mmol/l)	8.9 ± 1.5	8.4 ± 1.1
Serum 3-hydroxybutyrate (mmol/l)	6.35 ± 0.97	6.53 ± 0.87
Serum lactate (mmol/l)	1.60 ± 0.45	1.71 ± 0.27
Serum pyruvate (mmol/l)	0.12 ± 0.03	0.13 ± 0.02
Serum potassium (mmol/l)	5.1 ± 0.2	5.4 ± 0.2
Serum sodium (mmol/l)	139 ± 1	138 ± 2
Serum urea (mmol/l)	4.6 ± 0.6	7.5 ± 1.3

Data are means ± SE.

which insulin is administered at a constant rate until normalization of blood glucose (<10 mmol/l) and then administered at a reduced rate until clinical recovery.

RESEARCH DESIGN AND METHODS

Patients

Patients presented either through the accident and emergency department or after telephone consultation with their general practitioner. The diagnosis of diabetic ketoacidosis was based on clinical features of uncontrolled diabetes requiring emergency hospital admission, venous blood pH <7.25 or blood bicarbonate <16 mmol/l, and capillary blood 3-hydroxybutyrate >1.5 mmol/l. A total of 22 patients meeting these criteria were randomized either to the new extended insulin regimen (n = 12) or to a conventional insulin regimen (n = 10).

Treatment protocols

Initial treatment was the same for both groups with rehydration, electrolyte replacement, and insulin (human Actrapid; Novo Laboratories, Basingstoke, U.K.). At diagnosis, 20 U insulin was administered intramuscularly, and within 1 h a continuous intravenous insulin infusion was commenced to deliver 5 U/h. Insulin for infusion was prepared in 0.9% normal saline (1 U/ml) and 10 ml of the infusate discarded after filling syringes and tubing to minimize the effects of insulin adsorption to the tubing (23,26). The insulin infusion was continued at 5 U/h until capillary blood glucose fell to ≤10 mmol/l. Thereafter treatment differed for the two groups.

Extended regimen after achievement of near-normoglycemia. Intravenous insulin was continued at a constant rate of 5 U/h along with 20% glucose at a variable rate that maintained capillary blood glucose between 5 and 10 mmol/l, until capillary blood 3-hydroxybutyrate fell to <0.5 mmol/l. At this point, the insulin and 20% glucose infusions were stopped, and 500 ml of 5% glucose containing 8 U insulin was infused over 6 h. Additional subcutaneous insulin was given at four hourly intervals to maintain blood glucose at <10 mmol/l. With clinical improvement and oral feeding, regular subcutaneous insulin was recommenced and intravenous fluids discontinued.

Conventional regimen after near-normoglycemia. After attainment of near-normoglycemia, patients were changed to 5% glucose and insulin infusion (500 ml of 5% glucose containing 8 U insulin over 6 h). Additional subcutaneous insulin was given as necessary to maintain blood glucose <10 mmol/l. With clinical improvement, patients were transferred to oral feeding and regular subcutaneous insulin.

Biochemical measurements

From presentation until discontinuation of intravenous fluids, capillary blood was obtained hourly for measurement of glucose and 3-hydroxybutyrate concentrations. Venous blood was drawn for glucose, pH level, electrolytes, and 3-hydroxybutyrate at the following times: presentation, 2 h, and then every 3 h until near-normoglycemia, at which point a further sample was drawn. After near-normoglycemia, further samples were drawn at 2, 6, 12, and 24 h. Other investigations were carried out as clinically indicated.

Blood 3-hydroxybutyrate was measured as previously described using a reagent strip and bedside-reflectance meter (Ketofilm and Ketometer; Sanwa Kagaku Kenkyusho, Nagoya, Japan) (25,27,28). Serum 3-hydroxybutyrate was measured using a commercially available reagent kit (Randox Laboratories, Crumlin, Northern Ireland, U.K.) on a Cobas-Bio centrifugal analyzer (Hoffmann, La Roche, Basel, Switzerland). Other biochemical analyses were performed using standard techniques.

Between-batch coefficients of variation for 3-hydroxybutyrate measurements were 6.1 and 2.3% for the reagent strips and aqueous assay, respectively, at mean 3-hydroxybutyrate concentrations of 1.16 mmol/l. Validation studies carried out in our unit have demonstrated a close correlation between the ketofilm/ketometer system and the aqueous enzymatic assay (r = 0.97, $P < 0.05$) (25).

Ethical considerations

The study protocol was approved by the Research Ethics Committee of the Queen's University of Belfast. All patients gave informed consent. Since both protocols were identical until the capillary blood glucose had fallen to <10 mmol/l, it was possible to obtain consent after treatment had been initiated so that all patients were lucid and alert at the time of giving their consent.

Statistical analysis

Baseline (t_0) was taken as the time point at which blood glucose became <10 mmol/l because it was at this point that the protocols diverged. The main endpoints studied were improvement in ketosis and acidosis. To avoid repeated analysis of serial measurements of these main outcomes, two summary outcome measures were selected to represent improvement in each (29).

Summary measures for improvement in 3-hydroxybutyrate were *1*) time taken for normalization of blood 3-hydroxybutyrate (i.e., levels <0.5 mmol/l) after t_0 and 2) area under the curve of serum 3-hydroxybutyrate against time, for 24 h after t_0.

Table 2—*Measurements at achievement of near-normoglycemia (t_0)*

	Conventional insulin regimen	Extended insulin regimen
Plasma glucose (mmol/l)	8.4 ± 0.8	9.6 ± 0.4
Venous blood pH	7.21 ± 0.03	7.19 ± 0.03
Blood bicarbonate (mmol/l)	12.7 ± 1.6	12.7 ± 1.5
Serum 3-hydroxybutyrate (mmol/l)	4.53 ± 0.67	2.82 ± 0.41*
Serum potassium (mmol/l)	4.6 ± 0.3	5.0 ± 0.2
Serum sodium (mmol/l)	144 ± 2	143 ± 2
Serum phosphate (mmol/l)	0.86 ± 0.16	0.51 ± 0.12
Serum magnesium (mmol/l)	0.88 ± 0.06	0.78 ± 0.07
Serum urea (mmo/l)	3.8 ± 0.5	5.8 ± 0.9

Data are means ± SE. *P = 0.048 vs. conventional.

Before analysis, logarithmic transformation of these variables was performed so that the data approximated a normal distribution. At t_0, there was an unexpected difference in serum 3-hydroxybutyrate between the two groups. In addition, mean age was somewhat higher in the extended treatment group. To take account of these differences between the groups in the comparison of variables measuring ketosis resolution, analyses of covariance were performed with outcome measures *1*) and *2*) above (log scale) as dependent variables, and age and 3-hydroxybutyrate at t_0 as confounding variables (30). This enabled the comparison of treatment regimens to be adjusted for the effects of confounders both individually and simultaneously. The validity of the analyses of covariance was assessed by checking that the relationship between the response variables and each confounder in the conventional treatment group was parallel to the corresponding relationship in the extended treatment group

Blood bicarbonate levels at two defined times after t_0 (6 and 12 h) were used as indicators of improvement in acidosis. Other biochemical parameters were compared at various time points after t_0. Comparisons of these data between groups were made using the Mann-Whitney U test. Significance was taken as $P < 0.05$. All statistical tests were carried out on a personal computer using the statistical package software SPSS for Windows.

RESULTS — Patient characteristics and biochemical parameters at presentation are shown in Table 1. There were no statistically significant differences between groups, though those allocated to the extended insulin regimen tended to be older (P = 0.07) with a longer duration of diabetes and had slightly higher plasma glucose and serum urea concentrations. Near-normoglycemia was achieved slightly later with the extended insulin regimen (5.1 ± 1.0 vs. 3.4 ± 0.4 h; P = 0.3), at which point, 3-hydroxybutyrate was lower in this group (Table 2). Elevation of blood 3-hydroxybutyrate (>0.5 mmol/l) persisted for 5.9 ± 0.8 h after correction of hyperglycemia in those treated using the extended insulin regimen, compared with 21.8 ± 3.4 h in the conventionally treated group. This difference was statistically significant, even after adjustment for the differences in age and 3-hydroxybutyrate levels at baseline (Table 3). The area under the curve of 3-hydroxybutyrate against time, taken as a measure of exposure to 3-hydroxybutyrate over the 24 h after achievement of near-normoglycemia was significantly reduced with the extended insulin regimen (24.9 ± 3.8 vs. 55.9 ± 6.7 mmol · l^{-1} · h^{-1}). Again, this difference remained statistically significant after adjustment for baseline differences (Table 3).

The blood bicarbonate levels at 6 and 12 h after correction of hyperglycemia, taken as a measure of acidosis resolution, tended to be higher with the extended insulin regimen, but this did not reach statistical significance (Table 4). Other biochemical parameters after achievement of normoglycemia are summarized in Table 5. Plasma glucose was adequately controlled in both groups, and there was no difference in potassium levels between the two treatments. Serum phosphate concentrations at 2 and 6 h after achievement of normoglycemia were significantly lower in patients randomized to the extended insulin regimen.

CONCLUSIONS — This study addresses the issue of insulin administration after correction of hyperglycemia in the treatment of diabetic ketoacidosis. We have shown that an extended insulin regimen, involving continuation of insulin at 5 U/h until attainment of normal blood 3-hydroxybutyrate concentrations, produces a more effective resolution of ketosis compared with a more conventional regimen. Associated with this, there was a nonsignificant trend toward more rapid resolution of acidosis.

Our study was designed so that biochemical recovery after attainment of near-normoglycemia could be compared between the two regimens. Baseline (t_0) was therefore taken as the time when near-normoglycemia was achieved (blood glucose ≤10 mmol/l) rather than at presentation. There was a significant difference in 3-hydroxybutyrate levels between the groups at t_0, possibly related to the fact that patients allocated to the extended regimen required slightly longer to achieve normoglycemia. Therefore by t_0, they had received slightly more

Table 3—*Resolution of ketosis after achievement of near-normoglycemia (t_0)*

Outcome measure	Ratio extended/conventional regimens (95% CI)	P value
Time from t_0 until blood 3-hydroxybutyrate <0.5 mmol/l (h)		
Nonadjusted	0.30 (0.16–0.54)	0.0004
Adjusted for serum 3-hydroxybutyrate level at t_0	0.44 (0.25–0.76)	0.006
Adjusted for serum 3-hydroxybutyrate level at t_0 and age	0.42 (0.24–0.76)	0.006
Area under curve of serum 3-hydroxybutyrate from 0–24 h after t_0		
Nonadjusted	0.43 (0.27–0.69)	0.001
Adjusted for serum 3-hydroxybutyrate level at t_0	0.54 (0.33–0.88)	0.02
Adjusted for serum 3-hydroxybutyrate level at t_0 and age	0.58 (0.35–0.94)	0.03

See text for actual data.

Table 4—*Resolution of acidosis after achievement of near-normoglycemia (t_0)*

	Conventional insulin regimen	Extended insulin regimen	*P* value
Bicarbonate levels 6 h after t_0 (mmol/l)	16.0 ± 1.3	18.6 ± 0.6	0.09
Bicarbonate levels 12 h after t_0 (mmol/l)	16.5 ± 1.2	19.0 ± 0.7	0.08

Data are means ± SE.

insulin and intravenous fluids. Even after adjustment for this baseline difference, the extended insulin regimen clearly resulted in a more rapid lowering of 3-hydroxybutyrate levels. Moreover, the time taken from initial presentation until normalization of 3-hydroxybutyrate was significantly shorter with the extended regimen (10.8 ± 1.1 vs. 25.2 ± 3.7 h; $P = 0.002$). This latter analysis avoids the confounding effects of differences in 3-hydroxybutyrate at t_0, since at presentation these differences did not exist.

By chance, patients randomized to the extended insulin regimen were somewhat older ($P = 0.07$), with a longer duration of diabetes. Statistical analysis using age as a confounding variable (in addition to 3-hydroxybutyrate at t_0) indicated only a small influence on main outcome measures of ketosis resolution (Table 3). Further analysis using duration of diabetes as an additional confounder had minimal effect on outcome measures. Plasma glucose and serum urea (but not 3-hydroxybutyrate) were nonsignificantly higher in the extended group at presentation (Table 1), possibly reflecting an age-related delay in seeking medical advice.

More effective resolution of ketosis may be of clinical importance for two reasons. First, one might expect a parallel effect on resolution of acid-base disturbance. Our results demonstrated a trend toward more rapid restoration of bicarbonate levels with the extended regimen, though this did not reach statistical significance. Second, ketones may contribute to other metabolic abnormalities in diabetic ketoacidosis, including insulin resistance, which is evident at presentation and persists for several days after initial treatment (8,31–35). More effective resolution of ketosis may therefore lead to an improvement in insulin sensitivity during this early recovery period allowing earlier reintroduction of normal insulin therapy, which could potentially shorten hospital stay (36).

The main mechanism by which insulin lowers 3-hydroxybutyrate in diabetic ketoacidosis is by suppression of hepatic production of ketone bodies (7). Insulin levels achieved using a low-dose insulin regimen in ketoacidosis are high with reported levels exceeding 100 mU/l (37). Such levels are thought to achieve maximum suppression of ketogenesis (8). The basic rate of insulin administration with our conventional regimen after achievement of normoglycemia was ~1.3 U/h, though additional boluses were given subcutaneously if the blood glucose exceeded 10 mmol/l. Evidently, the insulin levels achieved with this rate of administration were not sufficient to exert a maximal effect upon ketone metabolism at this particular stage of recovery from ketoacidosis.

In addition to extra insulin, the extended regimen also involved administration of 20% glucose after attainment of normoglycemia. It could be argued that this, rather than the extra insulin, was responsible for the improvement in ketone body resolution. One prospective study (38) demonstrated a more rapid lowering of ketone bodies using 10 vs. 5% glucose infusion in diabetic ketoacidosis. However, additional insulin was given with the 10% glucose infusion, making it difficult to conclude that the higher concentration of glucose was responsible for the more rapid disappearance of ketones. While it is possible that the 20% dextrose given with our extended insulin regimen had some effect on ketone metabolism, it seems more plausible that extra insulin was responsible for the beneficial effects of the extended regimen. In any case, from a clinical standpoint, a regimen involving extra insulin will necessitate extra glucose and vice versa in order to control blood glucose levels.

Our new extended insulin regimen serves as a model for delivering extra insulin (and glucose) after correction of hyperglycemia in the treatment of diabetic ketoacidosis. If any such regimen is to be adopted for routine clinical use, it must not only be effective but also easy to implement at ward level. The ability to monitor blood 3-hydroxybutyrate regularly is essential and can be done using a bedside-reflectance meter (25,39). In practice, a single capillary blood sample is sufficient to allow measurement of both glucose and 3-hydroxybutyrate using bedside-reflectance meters, and minimal extra nursing input is required. Estimation of urinary ketones is not an adequate substitute since urinary output may be irregular and the predominant ketone body present,

Table 5—*Electrolytes (mmol/l) over 24 h after achievement of near-normoglycemia (t_0)*

	Hours after t_0			
Insulin regimen	2	6	12	24
Glucose				
Conventional	6.5 ± 1.1	7.0 ± 0.7	8.5 ± 1.1	9.5 ± 1.0
Extended	11.0 ± 0.7*	8.4 ± 1.0	7.3 ± 0.8	9.2 ± 1.0
Potassium				
Conventional	4.5 ± 0.2	4.5 ± 0.2	4.2 ± 0.2	4.2 ± 0.1
Extended	4.6 ± 0.2	4.4 ± 0.1	4.2 ± 0.1	4.3 ± 0.1
Sodium				
Conventional	143 ± 2	140 ± 2	137 ± 1	137 ± 1
Extended	140 ± 1	141 ± 1	138 ± 1	138 ± 1
Phosphate				
Conventional	0.77 ± 0.11	0.72 ± 0.10	0.63 ± 0.11	0.55 ± 0.10
Extended	0.46 ± 0.08†	0.42 ± 0.09‡	0.49 ± 0.07	0.61 ± 0.08
Magnesium				
Conventional	0.85 ± 0.05	0.81 ± 0.06	0.75 ± 0.04	0.76 ± 0.04
Extended	0.80 ± 0.04	0.82 ± 0.02	0.77 ± 0.03	0.74 ± 0.02
Urea				
Conventional	3.4 ± 0.4	2.9 ± 0.3	2.2 ± 0.2	2.0 ± 0.2
Extended	4.9 ± 0.9	3.9 ± 0.8	3.4 ± 0.6	2.6 ± 0.4

Data are means ± SE. *$P = 0.003$ vs. conventional; †$P = 0.03$ vs. conventional; ‡$P = 0.04$ vs. conventional.

3-hydroxybutyrate, is not detected by the nitroprusside reaction (22,40). Furthermore, concurrent medication may produce misleading results (41).

A further practical consideration regarding our new insulin regimen is the administration of 20% dextrose to avoid hypoglycemia after correction of hyperglycemia. Most patients in our study had not been adequately rehydrated at this stage, and further infusion of normal saline was required. In practice, the 20% dextrose was "piggy-backed" onto the normal saline infusion, with the advantage that the dextrose was considerably diluted and potential venous irritation avoided. Minimal extra medical input was required to control the rate of 20% dextrose administration, which was adjusted on an hourly basis. Further experience with the regimen would allow construction of a simple flow chart to simplify this aspect of treatment.

While no significant problems were encountered with the extended insulin regimen, the effect on phosphate levels is a source of concern. Theoretically, the more-marked hypophosphatemia observed with the extended insulin regimen could adversely affect recovery of red cell 2,3-diphosphoglycerate levels and hence oxygen delivery (21). Most current protocols do not recommend phosphate administration in the treatment of ketoacidosis (20,21), as controlled studies (with similar degrees of hypophosphatemia to that observed with our extended insulin regimen) have not shown it to be of benefit (42,43). In addition, there are definite risks associated with too rapid administration (44). If a more prolonged insulin regimen such as ours were to be adopted, significant hypophosphatemia during treatment is a potential problem, though its clinical importance is uncertain (6,19). Nevertheless, it would seem prudent to measure phosphate levels during treatment and review currently held positions on phosphate administration.

In summary, we have demonstrated that a new extended insulin regimen, involving low-dose insulin at a constant rate until normalization of blood 3-hydroxybutyrate, produced a more effective resolution of ketosis than that achieved with a more conventional regimen, in which the rate of insulin was reduced at achievement of normoglycemia. The new regimen described was not only effective, but also simple and safe to implement in a busy ward setting.

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