Original Articles

Diabetic Ketoacidosis During Long-Term Treatment with Continuous Subcutaneous Insulin Infusion

NORMAN R. PEDEN, M.R.C.P., JAN T. BRAATEN, F.R.C.P., AND J. B. RALPH McKENDRY, F.R.C.P.

During 1880 patient-months of treatment with continuous subcutaneous insulin infusion in 101 patients with IDDM, 36 episodes of acute, severe loss of glycemic control, including 29 with significant ketoacidosis, occurred in 20 patients. Fifteen episodes were attributable to failure of insulin delivery to the patient while 13 were precipitated by infection. Insufficiently frequent blood glucose monitoring, failure by patients to detect mechanical and technical problems with infusion systems, failure to adhere to "sick day" regimens, and delay in seeking medical help all contributed to the progression of a number of episodes. Thirst, nausea, and vomiting were the common clinical manifestations of decompensation; and the degree of acidemia was often mild in relation to the degree of hyperglycemia. Response to conventional management was usually prompt. DIABETES CARE 7: 1–5, JANUARY–FEBRUARY 1984.

Continuous subcutaneous insulin infusion (CSII) in association with frequent monitoring of blood glucose has been shown, during short- and medium-term studies, to be capable of producing overall improvement in control of glycemia in patients with insulin-dependent diabetes mellitus (IDDM).[1-9] Pumped insulin delivery is being increasingly used in managing IDDM in North America[10] and elsewhere and results of longer-term experience with large groups of patients are beginning to appear.[11-13]

This report addresses the problem of acute, severe loss of glycemic control during treatment of a large group of subjects with IDDM by CSII.

PATIENTS AND PROCEDURES

Studies to assess the role of CSII in long-term treatment of IDDM began at the Ottawa Civic Hospital in June 1980 and by the end of May 1983 had involved 101 patients and 1880 patient-months of pumped insulin delivery. These patients had a range of educational backgrounds although 50% had attended college or university after high school. Likewise, occupations included housewife, telephone linesman, computer programmer, and physician; 50% of our patients held professional or managerial positions. In all cases institution of CSII was undertaken in hospital. Patients participated in an education program that consisted of verbal instruction from medical and metabolic ward nursing and dietetic staff and written manuals specifically prepared for pump users in our hospital. Recently, audiovisual programs have also been used. Patients were only discharged from hospital when medical staff were satisfied that they had a good grasp of pump therapy and blood glucose monitoring and their interdependence, and that patients could react appropriately should problems arise. Algorithms were provided for optimization of blood glucose control at home with target blood glucose levels of 70–120 mg/dl fasting and before meals. Patients were also instructed on appropriate sick day regimens before discharge. On discharge, patients were asked to keep in frequent contact with their physician by telephone for both insulin adjustment and troubleshooting. Follow-up appointments were individualized depending on progress but were usually at 2, 4, and 6 wk initially and less frequently thereafter. Patients were asked to telephone their physician immediately should any problems develop and in addition were given a telephone number at the hospital for advice from medical personnel on a round-the-clock basis.

On discharge, patients were asked to monitor their blood glucose four times daily. Over the longer term the patients averaged three tests daily ranging from one to eight.

Up to the end of May 1983, 20 patients had experienced a total of 36 episodes of acute loss of glycemic control requiring hospital management; the last such episode included in this report occurred in mid-January 1983. Eleven patients had a single episode each, five had two episodes, three patients had three episodes each, and one patient had six ep-

isodes. Six of these patients had never had diabetic ketoacidosis (DKA) before the institution of CSII while 12 had experienced four or more episodes before starting CSII. The duration of CSII before the first episode averaged 5 mo (range: 0.5–15 mo) but in five cases was less than 1 mo. Characteristics of these patients are summarized in Table 1. Several models of syringe-type insulin pumps were used in this group of patients as indicated in Table 2, and this distribution is typical of our population as a whole with the majority of patients using the Autosyringe AS6C or AS6C U100 (AutoSyringe, Inc., Hooksett, New Hampshire).

TABLE 2
Insulin pumps used (and manufacturers) by patients in study group

Manufacturer	No. users
Autosyringe (Hooksett, New Hampshire)	
AS2C	3
AS6C	9
AS6C-U100	5
Mill Hill Infuser (Muirhead Medical Products, London, United Kingdom)	
MH 1001	1
Cardiac Pacemakers Inc. (St. Paul, Minnesota)	
CPI 9100	2

FACTORS PRECIPITATING LOSS OF GLYCEMIC CONTROL

As seen in Table 3, the most common cause of loss of control was interruption of insulin delivery due to mechanical or technical problems. Of 15 such episodes, 3 were due to failure of a pump component, including a fractured syringe cradle on an Autosyringe AS6C pump, breakdown of the pumping mechanism of a Mill Hill infuser (Muirhead Medical Products, London, United Kingdom), and failure of a battery charger of an Autosyringe AS2C pump. One episode resulted from insulin leaking from an infusion line that had cracked just distal to the luer lock of an Autosyringe AS6C system. This also occurred in another patient (not in this report) who noted the problem, changed the line, and was able to reduce her blood glucose from 700 mg/dl to normal at home by giving hourly insulin boluses.

In three instances, involving a CPI 9100 pump (Cardiac Pacemakers Inc., St. Paul, Minnesota), and an Autosyringe AS6C and AS6C U100, defective connections between the syringe and luer lock of the infusion line allowed insulin leakage when the infusion line was blocked. Circumstantial evidence suggested that a similar leak caused the single episode of DKA managed at another hospital. In the three cases seen at this hospital, the luer lock connection appeared to have been properly tightened by the patient. The importance of this leakage is that it decompresses the system and hence bypasses the alarm mechanism of the device failing to alert the patient of line blockage.

Four other episodes followed blockage of the indwelling needle, presumably due to precipitates forming in diluted insulin. Three patients presented with swollen and tender needle sites suggesting that inflammation limited absorption of insulin and/or increased the requirements.

Thirteen episodes of loss of control were associated with intercurrent infections including upper respiratory infections in seven cases and pneumonia in one. Two had posttraumatic cellulitis of an arm, two had influenza-like illnesses, which in one case was associated with mild hepatitis, and one episode occurred in a pregnant woman with a urinary tract infection. No definitive cause could be determined for seven episodes, including three in each of two patients. Both patients were highly intelligent women who had multiple admissions for ketoacidosis and severe hypoglycemia before starting CSII and were considered to merit the designation "brittle" diabetic patients.

Inappropriate action by the patient was a major factor in two cases. One disconnected his pump reasoning that he should not infuse insulin when not able to eat during a viral illness. Another allowed his syringe to become empty from giving extra boluses during a respiratory infection.

TABLE 1
Summary of characteristics of 20 patients in study group

Men:women	7:13
Age [mean (+ range) yr]	33.9 (19–61)
Duration IDDM [mean (+ range) yr]	18.2 (3–45)
No. with long-term complications	
Proteinuria (300 mg/day)	10
Background retinopathy	6
Proliferative retinopathy	7
Significant neuropathy	14

SELF-DIAGNOSIS AND MANAGEMENT BY THE PATIENT AT HOME

In 14 episodes the hyperglycemic decompensation developed overnight: the patient retired feeling well and awoke with symptoms of hyperglycemia. Of these 14 episodes a blood glucose of less than 180 mg/dl had been documented on retiring in eight cases and in three other cases before supper. In three cases no estimation had been made since the previous morning.

In 12 other episodes a rising blood glucose was documented before the development of symptoms but patients were unable to control this despite apparent adherence to the sick day regimen of two to three hourly glucose monitorings with extra boluses of insulin. In five of these episodes this was due to associated infection, but in seven of the episodes there was a mechanical problem not initially noted by the patient.

In six episodes a rising blood glucose was documented but the patients did not use the sick day regimen, while in four episodes occurring in two patients symptoms of hyperglycemia were the first warning of decompensation.

Patients had been unwell for a median duration of 12 h (range: 4–72 h) before seeking help.

TABLE 3
Summary of precipitating factors in 36 episodes of acute, severe, uncontrolled diabetes

Factors	No. patients affected
Failure of insulin delivery to patient	
Failure of pump component	3
Blocked line and luer lock defect	3 (? + 1)
Cracked infusion line	1
Blocked infusion line	4
Inflamed needle site	3
Displacement of needle	1
Total	15
Infection	
Upper respiratory tract infection	7
Pneumonia	1
Trauma/cellulitis	2
Presumed viraemic illness	2
Pregnancy/urine infection	1
Total	13
"Brittle" diabetes	6
Other	
Post general anesthesia	1
Cause unknown	1
Total	2

CLINICAL AND BIOCHEMICAL FEATURES

All episodes were accompanied by thirst, which was often described as intense. Another prominent feature was vomiting (28 episodes) or nausea without vomiting (7 episodes).

Biochemical findings on admission are summarized in Table 4. Serum glucose, sodium, potassium, urea nitrogen, and total venous CO_2 values (Astra-8 Discrete Analyzer, Beckman Inc., Fullerton, California) were obtained in all cases and blood pH and actual bicarbonate in 29.

Twenty-nine episodes were arbitrarily designated as showing significant DKA (actual bicarbonate or total $CO_2 < 15$ meq/L) while the remainder had primarily marked hyperglycemia (≧529 mg/dl) without significant acidosis.

Serum ketones as estimated by the nitroprusside method were positive at a dilution of ≧1:4 in 20 episodes of DKA while urine ketones were positive in an additional 8. Two of the nonacidotic patients had serum ketones positive at a 1:4 dilution while two had ketonuria.

Serum sodium was particularly low in the nonacidotic patients and exhibited a highly significant negative correlation with the serum glucose on admission ($r = -0.97$, $P < 0.01$). Three patients in the group with DKA had severe hyperkalemia ($K^+ = 7.5$ meq/L) and in two of these electrocardiographic abnormalities were noted.

MANAGEMENT

One nonacidotic patient (serum glucose 884 mg/dl on admission) in whom the infusion needle had become displaced during sleep was satisfactorily managed by changing the needle site and giving boluses of insulin via the pump every second hour. Otherwise patients were managed conventionally with intravenous saline (mean: 2.8 L/patient) before blood glucose falling to 250 mg/dl at which point the infusion fluid was usually changed to 5% dextrose and water. Intravenous potassium in total doses from 15 to 120 meq (mean: 55 meq) was given in 23 episodes.

Intravenous insulin was given as an initial bolus dose of 4–30 U (mean: 10 U) and thereafter insulin was infused intravenously at hourly rates of 2–10 U (mean: 5.2 U) until serum glucose fell to 250 mg/dl after which the infusion rate was reduced. Intravenous bicarbonate was used in five patients, and because of persisting hyperkalemia ($K^+ = 7.5$ meq/L), one patient received intravenous calcium gluconate. This person subsequently required hemodialysis because of worsening of chronic renal failure. One patient received lidocaine for hyperkalemia-associated ($K^+ = 7.5$ meq/L) ventricular dysrhythmia. Antibiotics were given to 10 patients because of known or suspected infection.

RESPONSE TO TREATMENT

Serum glucose fell by an average of 101 mg/dl/h and the mean interval from initiation of treatment until the serum glucose fell to 250 mg/dl was 5.4 h (range: 1–12). One nonacidotic patient whose initial blood glucose was 615 mg/dl became symptomatically hypoglycemic within 3 h of the start of treatment consisting of 2 L normal saline and only 4 U intravenous insulin. Before coming to the Emergency Department, however, this patient had taken four 10-U boluses of subcutaneous insulin via the pump at hourly intervals.

The mean interval until total venous CO_2 increased to ≧20 meq/L was 8 h (range: 2–24 h) in patients with DKA. Serum sodium normalized within 4 h. In general, serum po-

TABLE 4
Summary of biochemical findings on admission for ketoacidotic and nonacidotic groups of patients*

	DKA group (N = 29)	Nonacidotic group (N = 7)
Serum glucose (mg/dl)	757 ± 55 (427–1908)	743 ± 66 (529–939)
Total venous CO_2 (meq/L)	12 ± 0.6 (6–19)	21.7 ± 1.5 (17–29)
Actual HCO_3^- (meq/L)	9.3 ± 0.6 (4–15)	20.0 ± 1.3 (18–22)
pH	7.21 ± 0.02 (7.04–7.38)	7.35 ± 0.05 (7.31–7.45)
Serum Na^+ (meq/L)	131.9 ± 1.1 (120–141)	129.7 ± 1.3 (126–134)
Serum K^+ (meq/L)	5.5 ± 0.2 (4.2–7.5)	4.6 ± 0.3 (3.7–5.2)
Urea nitrogen (mg/dl)	40.4 ± 4.3 (21–131)	40.7 ± 5.4 (26–67)

*Results presented as mean ± SEM (and range).

tassium fell promptly with intravenous fluid and insulin treatment but stabilized by 2 h at a mean of 4.4 meq/L. Two patients, both of whom had been receiving long-term diuretic therapy for hypertension, developed mild hypokalemia with serum K^+ of 3.2 and 2.8 meq/L, respectively.

DISCUSSION

The widespread use of CSII[10] makes it important to be aware of the possibility of acute loss of glycemic control. Our experience indicates that this is a significant risk having encountered 36 such episodes during 1880 patient-months of pumped insulin delivery (one per 52 patient-months of treatment). This is broadly in accord with the Mason Clinic experience in which DKA was the most common complication of pump therapy occurring once per 100 mo of treatment.[14] That figure, however, includes only patients with pH < 7.3 on admission and would exclude the seven hyperglycemic nonacidotic episodes in our series. Combining our own and the Mason Clinic data suggests an incidence of DKA in pump patients of approximately 1 per 80 patient-months of treatment. We do not have valid figures for the incidence of DKA in a comparable group of diabetic patients on conventional treatment. We believe, however, that the incidence of DKA in our CSII series is higher than would have occurred with conventional treatment in the same group since six of our pump patients had never been in DKA before institution of CSII, and 42% of the episodes of metabolic decompensation were due to a problem related to the CSII mode of treatment.

A significant incidence of DKA has also been recorded in several smaller studies of CSII.[2,15–18] The Centers for Disease Control (Atlanta, Georgia) have attempted to assess mortality among pump users in selected states in the United States and found that 7 of 33 deaths occurred in DKA.[19] They concluded, however, that this figure was not more than expected.

Examination of the precipitating factors in metabolic decompensation in this series shows that in 42% of the episodes there was a problem related to CSII as a mode of insulin delivery. A number of our patients noted rising blood glucose values but failed to notice problems such as pump failure, line leaks, or blockage. Some of these mechanical problems such as the luer lock defect and cracked lines were, however, subtle and compounded the problem for the patient by bypassing the alarm mechanisms of the pumps. This merely emphasizes the point that when unexplained loss of glycemic control occurs, the infusion equipment should be removed and all aspects from battery to needle checked and, if necessary, replaced before reinsertion.

Our experience also suggests that in a significant number of episodes inadequate blood glucose monitoring played a major part in allowing metabolic deterioration to occur to the extent that hospital care was necessary. We have also found that in the longer term many patients will not perform the four daily blood tests that appear necessary for optimal glycemic control.[20] In another large series 25% of patients performed fewer than two capillary blood glucose monitorings per day.[13] This, therefore, will leave patients at risk of not detecting early a problem that may allow development of DKA.

Another worrying feature was the significant time delay (median: 12 h) between patients developing symptoms either of precipitating illness or of hyperglycemia and seeking medical help. The delay occurred despite all patients knowing that round-the-clock medical advice was available. This tendency by patients to delay in requesting help has been noted previously in both conventionally treated patients[21] and pump users.[22]

It may be that the apparent increased frequency of DKA in diabetic patients on pump treatment relates to the relative unfamiliarity of both physicians and patients with pump therapy and its complications. This problem may, therefore, decrease as awareness increases and patient education becomes more appropriate. Support for this hypothesis comes from the recent striking drop in the incidence of DKA in pump users in our hospital over a period during which we have been at pains to point out to patients the potential problems of pump therapy.

The metabolic decompensation that developed in these patients is remarkable mainly for the comparatively mild degree of acidemia that developed in relation to the striking hyperglycemia. The studies of Champion et al.[6] and Pickup et al.[23] on deliberate discontinuation of CSII have suggested that the blood glucose will plateau at a comparatively low value although ketone bodies will rise steadily. These studies were, however, carried out over a comparatively short period of time (up to 12 h) while many of our patients had been unwell for much longer periods by the time they came to the hospital. Another feature was a tendency toward severe hyperkalemia in some patients, including one with chronic renal failure. This has previously been noted in a group of brittle diabetic patients who decompensated during pump treatment.[15]

The response of our patients to conventional management with low-dose insulin and intravenous fluids was satisfactory and often with rapid rates of fall of blood glucose; insulin requirements were comparable to those of patients not using CSII who developed DKA.[24,25]

We conclude that CSII does not reduce the risk of hyperglycemic decompensation in patients with IDDM and may on occasion precipitate this because of specific problems in relation to the infusion equipment and its use by the patient. This underlines the importance of patient selection and education concerning pump therapy, the importance of availability of totally reliable infusion systems, and the need for early contact between patients and the diabetic care team when problems arise.

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From the Division of Endocrinology and Metabolism, Ottawa Civic Hospital, and the Department of Medicine, Faculty of Health Science, University of Ottawa, Ottawa, Ontario, Canada.

Address reprint requests to Dr. J. T. Braaten, Division of Endocrinology and Metabolism, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.

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