Insulin Therapy for Diabetic Ketoacidosis

Bolus insulin injection versus continuous insulin infusion

ERYN K. BUTKIEWICZ, BA
CYNTHIA L. LEIBSON, PHD
PETER C. O'BRIEN, PHD
PASQUALE J. PALUMBO, MD
ROBERT A. RIZZA, MD

OBJECTIVE — Despite widespread acceptance of continuous insulin infusion (CII) over bolus insulin injection (BII) for treatment of diabetic ketoacidosis (DKA), there are no population-based studies demonstrating whether CII has resulted in lower morbidity and mortality.

RESEARCH DESIGN AND METHODS — We addressed this issue using a provider-linked database and retrospectively reviewing the complete medical records of all incidence cases of diabetes among Rochester, Minnisota, residents from 1950 to 1989 with a discharge diagnosis of DKA. This population-based study describes the consequences of the widespread change in treatment modality outside the confines of a controlled clinical trial.

RESULTS — Among the diabetes incident cohort, there were 59 subjects with confirmed first episodes of DKA during 1950–1992; 29 of 30 subjects treated with BII occurred before 1970. All 29 CII cases occurred between 1976 and 1992. Sex, etiology, diabetes duration, and age at DKA were similar for the two groups. The proportion of obese individuals (BII = 2/28, CII = 8/21; $P = 0.01$) differed between groups. The CII group exhibited higher glucose values (BII = 24.9 ± 8.5 mmol/l, CII = 37.1 ± 15.1 mmol/l; $P = 0.002$) and lower bicarbonate values (BII = 7.7 ± 3.0 nmol/l, CII = 6.2 ± 2.9 nmol/l; $P = 0.04$) upon admission. The mean quantity of insulin administered was higher in the BII group than in the CII group (179 ± 140 and 99 ± 70 U, $P < 0.006$). The outcome of hypoglycemia occurred more frequently in the BII group than in the CII group (BII = 8/30, CII = 1/29; $P = 0.03$). The proportion with hypokalemia, neurological deficit, myocardial arrhythmia, or mortality did not differ significantly between groups.

CONCLUSIONS — Our findings suggest the introduction of CII was accompanied by a decreased incidence of hypoglycemia.

From the Department of Health Sciences Research (E.K.B., C.L.L., P.C.O.) and the Department of Internal Medicine, Division of Endocrinology (E.K.B., R.A.R.), Mayo Clinic, Rochester, Minnisota; and the Department of Internal Medicine, Division of Endocrinology (P.J.P.), Mayo Clinic, Scottsdale, Arizona.

Address correspondence and reprint requests to Robert A. Rizza, MD, Department of Internal Medicine, Division of Endocrinology, 5–164 W. Joseph, Mayo Clinic, Rochester, MN 55905.

Received for publication 9 September 1994 and accepted in revised form 16 March 1995.

BII, bolus insulin injection; CII, continuous insulin infusion; DKA, diabetic ketoacidosis; REP, Rochester Epidemiology Project.

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes resulting from severe insulin deficiency. Treatment consists of correction of fluid and electrolyte imbalance and insulin injection. Until the mid-1970s, insulin was generally given intravenously, intramuscularly, and/or subcutaneously as bolus injections. In 1972, Sönksen et al. (1) established that continuous infusion of low-dose insulin was an effective means of treating DKA. The advantages of low-dose infusion over large-dose injection were substantiated in controlled clinical trials (2–5). As a consequence, there was a widespread shift in DKA treatment from bolus insulin injection (BII) to continuous insulin infusion (CII). The extent to which the benefits of CII reported in these early studies translated to the community at large, however, has not been examined.

The present study takes advantage of the unique resources of the Rochester Epidemiology Project (REP) to address this question. All confirmed cases of new diabetes among Rochester, Minnesota, residents in 1950–1989 were followed through 1992 for diagnosis of DKA. Individuals treated with BII (primarily from 1950 to 1976) were compared with individuals treated with CII (primarily from 1976 to 1992) for mortality and morbidity following DKA.

RESEARCH DESIGN AND METHODS

— The community of Rochester is well suited for population-based historical cohort studies of the type presented here. Use of medical care by community residents is concentrated among a handful of providers. Each provider uses a patient-based record system, whereby information from every encounter is maintained within a single dossier. The records can be accessed through diagnostic and surgical indexes maintained as part of REP (6).

The REP diagnostic index was used to retrieve the records of all Rochester residents with a diagnosis of diabetes

Table 1—*Treatment for DKA 24 h after admission*

	BII (n = 30)			CII (n = 29)		
	Number treated	Mean dosage	Median dosage	Number treated	Mean dosage	Median dosage
Insulin (U)						
IV Bolus	1	155	—	0	—	—
IV Bolus + SC Bolus	16	212	—	0	—	—
IV Bolus + SC Bolus + IM Bolus	2	280	—	0	—	—
SC Bolus	11	106	—	0	—	—
Insulin Drip	0	—	—	10	104	—
Insulin Drip + IV Bolus	0	—	—	12	95	—
Insulin Drip + SC Bolus	0	—	—	2	63	—
Insulin Drip + IV Bolus + SC Bolus	0	—	—	4	108	—
Insulin Drip + SC Bolus + IM Bolus	0	—	—	1	73	—
Total insulin	30	179	145	29	99	77
Saline (l)	30	5.5	5.5	29	6.4	5.9
Bicarbonate (mEq)	9	88	88	12	97	88
Potassium (mEq)						
KCl	9	91	—	12	92	—
KPO_4	14	93	—	2	76	—
KCl + KPO_4	1	150	—	8	188	—
KPO_4 + Other	0	—	—	2	303	—
KCl + KPO_4 + Other	0	—	—	1	147	—
Total Potassium	24	94	90	25	142	131

IM, intramuscular; IV, intravenous; SC, subcutaneous.

or related disorder during the period of 1950–1989. All potential subjects were screened by a trained nurse abstractor under supervision of an endocrinologist. Subjects were confirmed as having diabetes using National Diabetes Data Group criteria. The criteria for diagnosis of diabetes and for classification by clinical type have been described in detail elsewhere (7,8). Confirmed cases of patients who resided in Rochester for at least 1 year before diagnosis were included in the incident cohort. The study was limited to incidence cases to assure identification of the first episode of DKA and to avoid potential bias due to selective survival.

The 2,179 incidence cases of diabetes during the period of 1950–1989 were followed through 1992 for a discharge diagnosis of DKA or diabetic coma. Records were reviewed to confirm the diagnosis of the first episode of DKA. Criteria for DKA included admission bicarbonate ≤15 nmol/l, urine or serum ketones, and glucose value ≥11.1 mmol/l (200 mg/dl). Two patients were excluded due to possible lactic or alcohol acidosis or because they were younger than 2 years of age.

Abstracted variables included sex; clinical type, age at diagnosis, and duration of diabetes; and height, weight, and type of treatment at DKA episode. Etiology of DKA was classified as infection, insulin error, use of glucocorticoids, myocardial infarction, diabetes onset, or unknown. The outcomes of interest included death before discharge, hypoglycemia, neurological deficit, hypokalemia, and myocardial arrhythmia.

Statistical analysis

Because data were highly skewed, nonparametric methods were used throughout. Continuous variables were analyzed using Wilcoxon's rank-sum test. Dichotomous variables were analyzed using chi-squared or Fisher's exact test. Multivariable analyses were not performed due to limited sample size. All statistical tests were two-tailed; $P \leq 0.05$ was considered significant.

RESULTS

Patient characteristics

There were 59 confirmed first episodes of DKA from 1950 through 1992. Thirty individuals received BII only; all but one episode occurred before 1976, and one occurred in 1991. The remaining 29 individuals were treated with CII between 1976 and 1992. Of the CII group, 25 were also treated with bolus injection, typically upon admission.

Insulin dosage, injection site, method of administration, and additional therapies for each treatment group are presented in Table 1. The mean insulin dosage in the first 24 h for the CII group was 55% of that for the BII group (P = 0.006). Among people supplemented with potassium, the proportion receiving KPO_4 alone differed between groups (14/24 vs. 2/25, $P < 0.001$); however, the

Table 2—*Clinical characteristics of patients with DKA*

	BII	CII
n	30	29
Sex (Female)	17/30	16/29
Mean (median) age at diabetes onset	27 (21)	34 (20)
Mean (median) age at first DKA episode	31 (23)	40 (34)
Mean (median) duration of diabetes (years)	4 (2)	6 (3)
Clinical type (I)	19/30	21/29
Obese subjects	2/28	8/21
Mean (median) length of illness prior to admission (days)	8 (4)	4 (2)

Obesity is defined as >120% of ideal weight or obesity mentioned by clinician, $P = 0.01$, Fisher's exact test.

proportion receiving any KPO_4 did not differ (15/24 vs. 13/25; $P = 0.45$).

The groups did not differ with respect to demographic and clinical characteristics except for a higher proportion of obese subjects in the CII relative to the BII group (Table 2). The difference in obesity reflects a temporal pattern observed for the entire Rochester diabetes cohort (C.L.L., personal communication) and for the U.S. population generally (9).

Multiple etiologies of DKA were recorded for seven patients in the CII group and four patients in the BII group. Infection and diabetes onset (either alone or in combination with other causes) were the most common etiologies in both groups. Insulin error was a precipitating factor in 21% of CII and 17% of BII cases. Etiology was unknown for three BII and seven CII patients.

The severity of DKA at admission was greater in the CII group than in the BII group as evidenced by higher glucose, lower bicarbonate (Table 3), and a greater proportion with mention of mental impairment (6/30 in BII vs. 14/29 in CII; $P = 0.02$). The proportion with 4+ urine ketones at admission was similar (21/29 in BII vs. 15/29 in CII; $P = 0.10$).

Adverse events

Outcomes following treatment are presented in Table 4. Eight people in the BII group met one or more criteria for hypoglycemia. The single case of hypoglycemia in the CII group was the initial patient in the cohort to be treated with CII; the person died of DKA 1 h after admission. Three of four and four of seven people with evidence of hypokalemia in the BII and CII groups, respectively, experienced hypokalemia after admission. Two patients from each group died before discharge. When all adverse events were considered together, the proportion of individuals experiencing any adverse event did not differ (11/30 in BII vs. 5/29 in CII; relative risk = 2.1, 95% confidence interval = 0.8–5.4).

CONCLUSIONS— Among 2,179 people in the 1945–1989 Rochester diabetes incidence cohort, there were 59 first episodes of diagnosed DKA between 1950 and 1992. Thirty were treated with bolus injection only. The other 29 patients all received continuous infusion. The mean insulin dosage administered to the CII group was 55% of that administered to the BII group. Despite greater severity of DKA at admission among the CII group relative to the BII group, a smaller proportion of the CII group experienced hypoglycemia. When all adverse events were combined, the proportion of individuals experiencing any adverse event did not differ between treatment groups.

Previous clinical trials found CII to be an efficacious, safe treatment for DKA with lower requirements for insulin and fewer episodes of hypoglycemia (2–5). Although the findings from these clinical trials were persuasive, the applicability of such studies to community practice was open to question. The studies were not population based. Subjects were not drawn from the entire community but consisted of people admitted to a referral setting who met defined criteria, and in at least three previous studies, the treatment groups were not mutually exclusive (2,5,10). Important issues such as small sample size, selection bias, selective survival, and nonindependent observations were not always addressed.

These limitations were minimized in this population-based study that focused on the first episode of DKA for incidence cases of diabetes among all residents of Rochester. However, retrospective "natural experiments" such as the one presented here also have important limitations. Although treatment groups were similar with regard to available demographic and clinical characteristics, control over potentially confounding variables was limited. Due to the small number of events, confidence intervals

Table 3—*Admission laboratory data*

	BII (n = 30)		CII (n = 29)	
	Mean	Median	Mean	Median
Glucose mmol/l (mg/dl)	24.9 (448)	23 (418)	37.1 (669)*	36 (650)
Plasma bicarbonate (nmol/l)	7.7	7.9	6.2†	5.0
Plasma potassium (mEq/l)	4.7	4.4	5.0	5.2
Plasma sodium (mEq/l)	135	135	135	137

Values for plasma potassium and plasma sodium were not available for three people in the BII Group. *$P = 0.002$, rank-sum test. †$P = 0.04$, rank-sum test.

Table 4—*Adverse events*

	BII (n = 30)	CII (n = 29)	Relative risks (95% confidence interval)
Hypoglycemia	8/30	1/29	7.73 (1.51–39.50)*
Hypokalemia	3/27	4/29	0.81 (0.20–3.30)
Arrhythmia	0	1/29	—
Neurological deficit	0	0	—
Mortality	2/30	2/29	0.97 (0.14–6.52)

Hypoglycemia is defined as glucose < 2.8 mmol/l (50 mg/dl), neuroglycopenic episode, or autonomic symptoms. Hypokalemia is defined as serum potassium <3.0 mEq/l other than that at admission . Arrhythmia is defined as documented supraventricular arrhythmia, ventricular tachycardia, or ventricular fibrillation. Neurological deficit is defined as clinician's mention of confusion, mental dullness, or other change attributed to hypoglycemia that responded to carbohydrate administration. *P = 0.03, Fisher's exact test.

for risk estimates were wide, and sophisticated statistical analysis was unwarranted. Treatment group assignment was largely a function of calendar year. The extent to which other factors, like changes in potassium supplementation and the introduction of human insulin and bedside glucose monitoring, or detection bias contributed to the findings is uncertain.

Whether human insulin causes more frequent hypoglycemia than animal insulin is controversial. We do not believe this is a factor in the present study because there were fewer episodes of hypoglycemia after 1979, despite more frequent use of human insulin after 1979. It could be argued that the lower rate of hypoglycemia in the CII relative to the BII group was attributable to increased documentation of less severe cases in the later time period. The finding that average severity at admission was greater among CII relative to BII, however, makes such detection bias unlikely. Similarly, any ascertainment bias for hypoglycemia attributable to the introduction of bedside glucose monitoring in 1986 would have been in the direction opposite to that found. However, because bedside monitoring potentially assists in determining proper insulin dosage, its introduction could explain the lower risk of hypoglycemia found in the CII group. It is unlikely that bedside monitoring alone contributed to findings reported here. The full effect of subcutaneous or intramuscular injection is not apparent until the insulin is completely absorbed. Because the time required for absorption following intramuscular or subcutaneous insulin injection is variable, particularly when the volume status of the patient is rapidly changing, the risk for hypoglycemia is not easily predicted in any given patient. Therefore, bedside monitoring of glucose would require scrupulous attention with subcutaneous or intramuscular injection.

In summary, this study showed that the risk of hypoglycemia following treatment for first episode of DKA among the Rochester, Minnesota, diabetes incident cohort was lower from 1976–1992 than from 1950–1976. The lower rate of hypoglycemia coincided with the use of CII and lower doses of insulin. The introduction of CII had no apparent effect on other adverse outcomes relative to the earlier method of insulin administration.

Acknowledgments— This study was supported in part by National Institutes of Health Grant DK-29953. C.L.L. was supported in part by a FIRST Award from the National Institute on Aging (AG-08729).

We wish to thank Rita Black and Jo Johnson for efforts in data abstraction. We also wish to thank David Turk, MD, for helpful discussions.

References

1. Sönksen PH, Srivastava MC, Tompkins CV, Onwabarro J: Growth hormone and cortisol responses to insulin infusion in patients with diabetes mellitus. *Lancet* 2:155–159, 1972
2. Pfeifer MA, Samols E, Wolter CF, Winkler CF: Low-dose versus high-dose insulin therapy for diabetic ketoacidosis. *South Med J* 72:149–154, 1979
3. Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AE: Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. *Diabetes Care* 3:15–20, 1980
4. Piters KM, Kumar D, Pei E, Bessman AN: Comparison of continuous and intermittent intravenous insulin therapies for diabetic ketoacidosis. *Diabetologia* 13:317–321, 1977
5. Lutterman JA, Adriaansen AAJ, van 't Laar A: Treatment of severe diabetic ketoacidosis. *Diabetologia* 17:17–21, 1979
6. Kurland LT, Molgaard CA: The patient record in epidemiology. *Sci Am* 245:54–63, 1981
7. Melton LJ, Palumbo PJ, Dwyer MS, Chu CP: Impact of recent changes in diagnostic criteria on the apparent natural history of diabetes mellitus. *Am J Epidemiol* 117: 559–565, 1983
8. Johnson DD, Palumbo PJ, Chu CP: Diabetic ketoacidosis in a community-based population. *Mayo Clin Proc* 55:83–88, 1980
9. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA* 272:205–211, 1994
10. Ellemann K, Soerensen JN, Pedersen L, Edsberg B, Andersen OO: Epidemiology and treatment of diabetic ketoacidosis in a community population. *Diabetes Care* 7:528–532, 1984