Is Subcutaneous Administration of Rapid-Acting Insulin as Effective as Intravenous Insulin for Treating Diabetic Ketoacidosis?

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From the Editor—Emergency physicians must often make decisions about patient management without clear-cut data of sufficient quality to support clinical guidelines or evidence-based reviews. Topics in the Best Available Evidence section must be relevant to emergency physicians, are formally peer reviewed, and must have a sufficient literature base to draw a reasonable conclusion but not such a large literature base that a traditional "evidence-based" review, meta-analysis, or systematic review can be performed.

[Ann Emerg Med. 2009;53:259-263.]

ABSTRACT

To determine whether intermittent subcutaneous administration of rapid-acting insulin is as effective as intravenous infusion of regular insulin for treating uncomplicated diabetic ketoacidosis, we performed a MEDLINE, EMBASE, and Cochrane Library search, using the key words "subcutaneous insulin AND intravenous insulin AND diabetic ketoacidosis; LIMIT humans and English." We also searched the references in these articles for additional studies. This search yielded a total of 35 articles, 4 of which directly addressed the question at hand. According to this review of the available evidence; subcutaneous administration of rapid-acting insulin analogs such as lispro is as effective and safe as intravenous infusion of regular insulin for the management of uncomplicated diabetic ketoacidosis. In addition, use of insulin analogs may confer an overall cost savings, obviating the need for infusion pumps and ICU admissions in certain institutions. Therefore, it would be safe and effective to use subcutaneously administered rapid-acting insulin analogues instead of intravenous regular insulin infusions for patients with uncomplicated diabetic ketoacidosis.

INTRODUCTION

Diabetes mellitus, second only to hypertension as the most common chronic condition of emergency department (ED) patients, can cause acute hyperglycemia and ketoacidosis, responsible for more than 1 million ED visits in 2005.[1] Traditionally (and more recently endorsed by the American Diabetes Association),[2] the treatment of diabetic ketoacidosis is accomplished by the administration of a low dose intravenous infusion of regular insulin that is initiated in the ED and continued in an ICU[3] setting for frequent insulin/fluid adjustments, glucose monitoring, and electrolyte assessment. Although insulin administration by any route is effective for treating diabetic ketoacidosis, intravenous insulin is preferred over subcutaneous and intramuscular insulin because it provides rapid, titratable glycemic control.[4,5] For example, subcutaneous regular insulin has an onset of action within 1 hour, peaks within 1 to 5 hours, and may last for 6 to 10 hours, whereas intravenous insulin acts within minutes and has a half-life of 9 minutes.[4] Within the past decade, rapid-acting insulin analogues (lispro [Humalog, Eli Lilly and Company, Indianapolis, IN], aspart [Novolog, Novo Nordisk Inc, Princeton, NJ], and glulisine [Apidra, Sanofi-Aventis, Bridgewater, NJ]) have been adopted preferentially for the inpatient treatment of hyperglycemia because of their more favorable pharmacokinetic profiles. When administered subcutaneously, these analogs have an onset of action within 10 to 20 minutes, peak within 30 to 90 minutes, and last approximately 3 to 4 hours.[6,7] Because intravenous insulin infusion requires ICU admission in some institutions and higher equipment (infusion pumps, additional intravenous access) and nursing costs, we searched the literature to determine whether intermittent subcutaneous use of these rapid-acting analogs might be as effective as intravenous insulin infusions in treating uncomplicated diabetic ketoacidosis.

SEARCH STRATEGY

A MEDLINE (mid-1960s to present), EMBASE, and Cochrane Library search was performed using the key words "subcutaneous insulin AND intravenous insulin; LIMIT humans and English." This search strategy yielded 35 articles. Bibliographic references in these articles were also reviewed to identify other pertinent literature. We identified 4 original studies that directly compared intravenous insulin infusion with intermittent subcutaneous rapid-acting insulin analogues for treating diabetic ketoacidosis. These studies focused primarily on lispro, the first commercially available rapid-acting insulin analogue.

ARTICLE SUMMARIES

Umpierrez et al[5]

This multicenter prospective, randomized, open, clinical trial compared regular intravenous insulin infusion with hourly

subcutaneous lispro in patients with uncomplicated diabetic ketoacidosis, defined by a plasma glucose level greater than 250 mg/dL, serum bicarbonate level less than 15 mEq/L, blood pH less than 7.3, serum ketone level at a dilution of greater than or equal to 1:4 by nitroprusside reaction, and serum β-hydroxybutyrate level greater than 31 mg/dL. Patients with persistent hypotension, heart failure, end-stage liver or renal failure, acute myocardial ischemia, comatose state, pregnancy, and dementia were excluded. Eligible patients were randomized to receive intravenous insulin (0.1 U/kg bolus followed by a continuous infusion of 0.1 U/kg/h) in an ICU or subcutaneous lispro (0.3 U/kg bolus followed by hourly injections of 0.1 U/kg) on a medical floor or step-down unit. Bed assignment was based not on severity of illness but on route of insulin administration. The outcome variables were time to resolution of ketoacidosis (serum bicarbonate level ≥18 mEq/L and venous pH >7.3), amount of insulin required, length and cost of hospital stay, and hypoglycemic episodes.

Compared with the intravenous insulin group, the subcutaneous lispro patients were similar in patient characteristics, including mean age (37±12 versus 39±14 years), sex (60% versus 65% male patients), race (75% versus 80% black), and duration of diabetes mellitus (6.7±5 versus 6.9±4 years), as well as biochemical characteristics, including mean initial glucose level (674±154 versus 611±264 mg/dL) and acidemia (mean pH 7.17±0.10 versus 7.19±0.08). Twenty patients were assigned to receive intravenous insulin, 10 were randomized to subcutaneous lispro on a general medical floor, and 10 received subcutaneous lispro in a step-down unit. There was no statistical difference between the 2 groups in their time to resolution of ketoacidosis (approximately 12 hours), the amount of insulin required, and number of hypoglycemic episodes (1 episode in each). Furthermore, there was no difference in the rate of decrease in plasma glucose levels and correction of acid-base characteristics. When the authors plotted the data over time for all characteristics, the curves for both treatment groups were parallel. Although there was no difference in the hospital length of stay, there was a 39% decrease in the cost of stay in the subcutaneous lispro group ($14,429±$5,243 versus $8,801±$5,549; $P<.01$).

The authors concluded that patients with uncomplicated diabetic ketoacidosis could be safely and effectively treated with subcutaneous lispro, with an added benefit of cost savings because subcutaneous administration of insulin did not require ICU admission.

Umpierrez et al[6]

This single-site, prospective, randomized, open, clinical trial compared intravenous insulin infusion with hourly subcutaneous aspart and 2-hour subcutaneous aspart in patients with uncomplicated diabetic ketoacidosis, defined by a plasma glucose level greater than 250 mg/dL, serum bicarbonate level less than 15 mEq/L, blood pH less than 7.3, serum ketone level at a dilution of greater than or equal to 1:4 by nitroprusside reaction, or serum β-hydroxybutyrate level greater than 3 mmol/dL. Patients with persistent hypotension, end-stage liver or renal failure, acute myocardial ischemia, pregnancy, and dementia were excluded. Eligible patients were randomized to receive intravenous insulin (0.1 U/kg bolus followed by a continuous infusion of 0.1 U/kg/h until a glucose level of 250 mg/dL was reached, and then reduced to 0.05 U/kg/h until resolution of diabetic ketoacidosis) in an ICU, subcutaneously 1 hour aspart (0.3 U/kg bolus, followed by hourly injections of 0.1 U/kg, and then reduced to 0.05 U/kg) or subcutaneously 2 hours aspart (0.3 U/kg bolus, followed by injections of 0.2 U/kg every 2 hours, and then reduced to 0.1 U/kg) on a medical floor or step-down unit. Bed assignment was based on route of insulin administration and not severity of illness. The outcome variables were time to resolution of ketoacidosis (serum bicarbonate level ≥18 mmol/L and venous pH >7.3), amount of insulin required, length of stay, and hypoglycemic episodes.

Forty-five patients were enrolled, with 15 patients in each group. The patient characteristics (mean age [36±8 versus 38±12 versus 40±13 years], sex [73% versus 67% versus 67% male patients], mean body mass index [27±6 versus 29±7 versus 27±7 kg/m^2]) and biochemical profiles (mean initial serum glucose [797±380 mg/dL versus 761±380 mg/dL versus 724±236 mg/dL], mean venous pH [7.14±0.09 versus 7.15±0.12 versus 7.11±0.17], and mean anion gap [24 in each]) were similar in the subcutaneously 1 hour aspart, subcutaneously 2 hours aspart, and intravenous insulin groups, respectively. In addition, there was no statistical difference between the 3 groups in their time to resolution of ketoacidosis (10±3 versus 10.7±3 versus 11±3 hours), the amount of insulin required (85±33 versus 94±32 versus 82±28 units), and number of hypoglycemic episodes (1 episode in each). There was also no difference in the rate of decrease in plasma glucose levels, correction of acid-base characteristics, and length of hospitalization. There were no deaths during the study period.

The authors concluded that patients with uncomplicated diabetic ketoacidosis may be safely and effectively treated with subcutaneous 1-hour or subcutaneous 2-hour aspart in a non-ICU setting.

Della Manna et al[7]

This Brazilian prospective, randomized, open, clinical trial compared intravenous insulin infusion with hourly subcutaneous lispro in children and adolescents with diabetic ketoacidosis, defined by a blood glucose level greater than 300 mg/dL, serum bicarbonate level less than 15 mEq/L, blood pH less than 7.3, and ketonuria greater than ++ on urine dipstick test (corresponds to moderate ketones in urine, though not a perfect qualitative measure). Patients requiring surgical procedures or undergoing treatment with glucocorticoid or immunosuppressive agents were excluded. Eligible patients were randomized to receive intravenous insulin (continuous infusion of 0.1 U/kg/h until the glucose level reached 250 mg/dL, and then given 0.15 U/kg subcutaneously every 4 hours for 24 hours) or subcutaneous lispro (0.15 U/kg every 2 hours until

Table. Summary of study results.

Study	No. of Patients	Inclusion Criteria	Exclusion Criteria	Time to Resolution of Diabetic Ketoacidosis, h		Total Insulin Required, Units		No. of Hypoglycemic Episodes		Hospital length of stay, days		Cost
				IV	SQ	IV	SQ	IV	SQ	IV	SQ	
Umpierrez[5]	40	Diabetic ketoacidosis Glucose >250 mg/dL Bicarbonate <15 mEq/L pH <7.3 +serum ketones β-hydroxybutyrate >3 mmol/L	Persistent hypotension Comatose state/ dementia Acute myocardial ischemia Heart failure End stage renal disease Anasarca Pregnancy	11±4	10±3	98±26	84±32	1	1	4±1	4±2	39% Less SQ
Umpierrez[6]	45	Diabetic ketoacidosis Glucose >250 mg/dL Bicarbonate <15 mEq/L pH <7.3 +serum ketones β-hydroxybutyrate >3 mmol/L	Persistent hypotension Acute myocardial ischemia End stage renal disease Hepatic failure Anasarca Dementia Pregnancy	11±3	10±3 (q 1 h) 10.7±3 (q 2 h)	82±28	85±33 (q 1 h) 94±32 (2 h)	1	1 (q 1 h) 1 (q 2 h)	4.5±3	3.4±3 (q 1 h) 3.9±5 (q 2 h)	N/A
Della Manna[7]	50	Diabetic ketoacidosis Glucose >300 mg/dL pH <7.3 Bicarbonate <15 mmol/L >++ ketonuria	Surgery required Use of glucocorticoids Immunosuppressed	12	18	0.28±0.19 Units/kg	0.37±0.24 Units/kg	6	4	N/A	N/A	N/A
Ersoz[8]	20	Diabetic ketoacidosis Glucose >250 mg/dL β-hydroxybutyrate >1.6 mmol/L pH <7.3 Bicarbonate <15 mmol/L +urine ketones	Persistent hypotension Hypothermia Glucose >600 mg/dL pH <7.00 Bicarbonate <10 mmol/L Severe concomitant illness	13.2±7.5	14.8±7	65.2±12.7	61.7±10.9	N/A	N/A	N/A	N/A	N/A

IV, Intravenous; *SQ*, subcutaneous.

the glucose level reached 250 mg/dL, and then given 0.15 U/kg every 4 hours for 24 hours) in the ED or the ICU. The outcome variables were time to resolution of ketoacidosis (serum bicarbonate level ≥15 mmol/L, venous pH >7.3, and anion gap <16 mmol/L), correction of blood glucose and acid-base characteristics, and hypoglycemic episodes.

Fifty patients were enrolled; 25 patients presenting with 30 diabetic ketoacidosis episodes were randomized into each group. Of the 60 diabetic ketoacidosis episodes, 57 were treated in the ED and 3 in the ICU. Compared with the intravenous insulin group, the subcutaneous lispro patients were similar in patient characteristics, including mean age (11±4 versus 12±3 years) and sex (68% versus 64% female patients), and biochemical characteristics, including mean initial glucose level (446 mg/dL for both), acidemia (pH 7.17±0.10 versus 7.18±0.10), and anion gap (22±7 versus 30±9). In both groups, the time to reach a glucose level of 250 mg/dL was similar, approximately 6 hours. Compared with the intravenous insulin patients, the subcutaneous lispro patients took longer to resolve their acidosis (18 versus 12 hours) and were more likely to receive bicarbonate therapy (6 versus 4 patients). There were 10 mild hypoglycemic episodes, 6 in the intravenous insulin group and 4 in the subcutaneous lispro group. There were no deaths or cases of cerebral edema.

The authors concluded that children and adolescents with uncomplicated diabetic ketoacidosis could be safely and effectively treated with subcutaneous lispro administered every 2 hours in a non-ICU setting. They attributed the slower resolution of acidemia in the subcutaneous lispro group to the increased interval of injections at every 4 hours.

Ersoz et al[8]

This Turkish study was a prospective, randomized, open trial that compared hourly subcutaneous lispro and intravenous insulin infusion for mild to moderate diabetic ketoacidosis, defined by serum glucose level greater than 250 mg/dL and less than 600 mg/dL, arterial pH less than 7.3, serum bicarbonate level less than 15 mmol/L, and positive ketonuria result. Patients with severe diabetic ketoacidosis (eg, persistent hypotension, hypothermia, glucose level >600 mg/dL, arterial pH <7.0, or serum bicarbonate level <10 mmol/L) were excluded. The subcutaneous lispro group received an intravenous bolus of regular insulin (0.15 U/kg), followed by hourly subcutaneous lispro (0.075 U/kg). The intravenous insulin group also received a bolus of regular insulin (0.15 U/kg), followed by a standard insulin infusion. Outcome variables included time to resolution of ketoacidosis (serum glucose level <200 mg/dL, bicarbonate level >18 mmol/L, venous pH >7.3, capillary hydroxybutyrate level <0.5 mmol/L, and negative urine ketone results), adverse drug reactions, and mortality.

Twenty patients were enrolled into the study, 10 in each group. Compared with the intravenous insulin patients, the subcutaneous lispro patients were slightly younger (mean age 39±20 versus 49±18 years), with more microvascular and macrovascular complications of diabetes (70% versus 40%), although the differences were not statistically significant. Their biochemical profiles (mean initial glucose [512.1±137.5 versus 555.7±42.9], mean pH [7.15±0.11 versus 7.18±0.12], and bicarbonate level [11.5±3.6 versus 10.8±5.7]) were similar. The subcutaneous lispro group was as good as the intravenous insulin group in their time to normalization of serum glucose (9.4±8.9 versus 12.7±7.5 hours), pH (8.2±5.6 versus 6.8±8.7 hours), and ketonuria (17.2±7.0 versus 22.3±10.9 hours). Plotting the outcome characteristics over time yielded parallel curves for all of the treatment groups. There were no hypoglycemic events or deaths during this study period.

Although this study was small and underpowered to find a difference, the authors concluded that uncomplicated diabetic ketoacidosis may be safely and effectively treated with subcutaneous lispro.

THE BOTTOM LINE

According to this review of the available data (Table), subcutaneous administration of rapid-acting insulin analogues such as lispro every hour (0.3 U/kg bolus; then 0.1 U/kg) or 2 hours (0.3 U/kg bolus; then 0.2 U/kg) may be a reasonable alternative to intravenous regular insulin infusion for treating uncomplicated diabetic ketoacidosis. Insulin analogues are as effective as intravenous insulin at normalizing glucose levels and other acid-base characteristics, with similar rates of hypoglycemia. Moreover, patients receiving subcutaneous insulin may be treated on the medical floors or in step-down units, which may provide an overall cost savings and improve ED patient flow when ICU beds are scarce. Finally, although the data provided support for our conclusions, they are based on a few small studies (with slightly different inclusion and exclusion criteria and definitions for resolution of diabetic ketoacidosis), focused on one particular analogue (lispro), and assume that intravenous insulin infusions require monitoring in intensive care settings. More important, the majority are manufacturer-sponsored studies, thereby introducing the potential for a conflict of interest. Despite these limitations, we conclude that it would be safe and effective to treat uncomplicated diabetic ketoacidosis with a subcutaneously administered rapid-acting insulin analogue.

doi:10.1016/j.annemergmed.2008.07.023

Supervising editor: Judd E. Hollander, MD

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

Publication date: Available online August 16, 2008.

Reprints not available from the authors.

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