Is a Priming Dose of Insulin Necessary in a Low-Dose Insulin Protocol for the Treatment of Diabetic Ketoacidosis?

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**OBJECTIVE** — The purpose of this study was to assess the efficacy of an insulin priming dose with a continuous insulin infusion versus two continuous infusions without a priming dose.

**RESEARCH DESIGN AND METHODS** — This prospective randomized protocol used three insulin therapy methods: 1) load group using a priming dose of 0.07 units of regular insulin per kg body weight followed by a dose of 0.07 unit kg⁻¹·h⁻¹ i.v. in 12 patients with diabetic ketoacidosis (DKA); 2) no load group using an infusion of regular insulin of 0.07 unit kg⁻¹·h⁻¹ without a loading dose in 12 patients with DKA, and 3) twice no load group using an infusion of regular insulin of 0.14 unit kg⁻¹·h⁻¹ without a loading dose in 13 patients with DKA.

Outcome was based on the effects of insulin therapy on biochemical and hormonal changes during treatment and recovery of DKA.

**RESULTS** — The load group reached a peak in free insulin value (460 μU/ml) within 5 min and plateaued at 88 μU/ml in 60 min. The twice no load group reached a peak (200 μU/ml) at 45 min. The no load group reached a peak (60 μU/ml) in 60–120 min. Five patients in the no load group required supplemental insulin doses to decrease initial glucose levels by 10%; patients in the twice no load and load groups did not. Except for these differences, times to reach glucose ≤230 mg/dl, pH ≥7.3, and HCO₃⁻ ≥15 mEq/l did not differ significantly among the three groups.

**CONCLUSIONS** — A priming dose in low-dose insulin therapy in patients with DKA is unnecessary if an adequate dose of regular insulin of 0.14 unit kg⁻¹·h⁻¹ (about 10 units/h in a 70-kg patient) is given.

Although positive therapeutic responses to low-dose insulin therapy have been established in adult patients with diabetic ketoacidosis (DKA) (1–8), none of these studies and guidelines for the treatment of DKA, including the American Diabetes Association (ADA) Consensus and Position Statements, has ever assessed or addressed the use of a continuous insulin infusion without a loading dose of insulin (9). In the current study, we used a dose of 0.14 unit kg⁻¹·h⁻¹ without a loading dose instead of the recommended 0.1 unit kg⁻¹·h⁻¹ with a loading dose. This insulin regimen was chosen because one study in a pediatric population used a dosing regimen of 0.1 unit kg⁻¹·h⁻¹ without a loading dose that resulted in a total plasma insulin level of 50–60 μU/ml (10). This level proved to be too low for optimal suppression of hepatic glucose output and optimal glucose uptake (11). In addition, bolus doses of insulin may result in hypokalemia as well as other undesirable effects (12), especially when used in a routine hospital setting.

The efficacy of low-dose insulin without a priming dose has not been established in a prospective randomized study (13). Thus, the following questions have remained unanswered in the treatment of DKA: 1) Is an insulin bolus needed before a continuous insulin infusion? 2) What is the optimal insulin infusion rate if a bolus dose is not used? and 3) What is the dose response of continuous insulin infusion used alone in regard to decremental changes in glucose, metabolic parameters, cortisol, and free fatty acids (FFAs)?

Therefore, we evaluated responses to three low-dose insulin regimens in 37 consecutive patients with DKA in a prospective randomized fashion to address these issues. Changes in plasma free insulin, serum potassium levels, and outcome recovery measures were assessed using a higher infusion dose (0.14 unit kg⁻¹·h⁻¹ without a bolus dose) compared with a lower infusion dose (0.07 unit kg⁻¹·h⁻¹) with and without a loading dose (0.07 unit/kg) of insulin.

**RESEARCH DESIGN AND METHODS** — Our criteria for the diagnosis of DKA included plasma glucose >250 mg/dl, HCO₃⁻ <15 mEq/l, pH <7.3, and moderate ketones in the urine or blood by the nitroprusside method. A total of 37 patients were prospectively randomly assigned to three groups as follows: 1) the load group consisted of 12 patients who received a loading dose of insulin at 0.07 unit/kg body weight followed by an infusion of 0.07 unit/kg body weight⁻¹·h⁻¹; 2) the no load group consisted of 12 patients who received only an intravenous infusion of insulin at a dose of 0.07 unit/kg body weight⁻¹·h⁻¹ without a loading dose; or 3) the twice no load group consisted of 12 patients who received an infusion of insulin at a dose of 0.14 unit/kg body weight⁻¹·h⁻¹ without a bolus dose. Responses to therapy were based on the time to achieve a glucose level of ≤250 mg/dl, bicarbonate of ≥15 mEq/l, and pH ≥7.3. All other modes of therapy (hydrating solution, KCl, and HCO₃⁻) were similar in the three groups and followed the recommendations of the first ADA position statement (6). All patients were seen in the emergency department of the Regional Medical Center at Memphis. Upon
Insulin for treatment of diabetic ketoacidosis

Table 1—Demographics and clinical data of 37 patients with DKA with three intravenous insulin protocols

|                     | Load          | No load       | Twice no load |
|---------------------|---------------|---------------|---------------|
| n                   | 12            | 12            | 13            |
| Age (years)         | 28.6 ± 2.3 (19–44) | 37.3 ± 4.2 (20–66) | 31.8 ± 2.8 (17–50) |
| Sex                 |               |               |               |
| Female              | 4             | 9             | 6             |
| Male                | 8             | 3             | 7             |
| Race                |               |               |               |
| Caucasian           | 4             | 0             | 4             |
| African American    | 8             | 12            | 9             |
| BMI (kg/m²)         | 22.1 ± 1.6    | 24.6 ± 2.6    | 22.1 ± 1.3    |
| Duration of diabetes (years) | 8.5 ± 1.7 | 5.6 ± 2.0 | 8.0 ± 2.5 |
| Treatment           |               |               |               |
| None                | 2             | 5             | 2             |
| Diet                |               |               |               |
| Insulin             | 10            | 7             | 9             |
| Precipitating factor |               |               |               |
| Lack of insulin     | 6             | 6             | 5             |
| Infection           | 3             | 4             | 5             |
| Other               | 3             | 2             | 3             |
| Blood pressure      |               |               |               |
| Systolic (mmHg)     | 125 ± 8       | 127 ± 8       | 128 ± 5       |
| Diastolic (mmHg)    | 66 ± 3        | 81 ± 4        | 82 ± 4        |
| Pulse (beats/min)   | 109 ± 3       | 108 ± 5       | 113 ± 6       |
| Respiratory rate (per min) | 27 ± 1.0 | 24 ± 1.0 | 29 ± 1.0 |
| Mental status       |               |               |               |
| Alert               | 9             | 5             | 5             |
| Drowsy              | 3             | 5             | 7             |
| Stupor              |               |               |               |
| Comatose            | 1             | 1             | 1             |

Data are means ± SEM, means ± SEM (range), or n.

Table 2—Biochemical and hormonal data at baseline and recovery of patients with DKA receiving three insulin protocols

|                     | Load          | No load       | Twice no load |
|---------------------|---------------|---------------|---------------|
| Sodium (mEq/l)      | 131 ± 2       | 137 ± 1.1     | 137 ± 3       |
| Potassium (mEq/l)   | 5.4 ± 0.3     | 4.0 ± 0.14    | 4.8 ± 0.2     |
| Bicarbonate (mEq/l) | 6.7 ± 0.7     | 17.8 ± 1.0    | 5.9 ± 0.8     |
| Glucose (mg/dl)     | 578 ± 64      | 162 ± 12      | 459 ± 38      |
| Blood urea nitrogen (mg/dl) | 29 ± 6  | 16.3 ± 3.8 | 21 ± 4       |
| Anion gap (mEq/l)   | 27 ± 1        | 11.3 ± 1.8    | 24 ± 2        |
| pH                  | 7.12 ± 0.03   | 7.3 ± 0.01    | 7.15 ± 0.03   |
| β-Hydroxybutyrate (mmol/l) | 10.5 ± 1.1 | 2.4 ± 0.9    | 8.8 ± 0.9     |
| Acetoacetate (mmol/l) | 2.5 ± 0.3    | 1.06 ± 0.19   | 2.6 ± 0.3     |
| Total ketones (mmol/l) | 13.0 ± 1.1 | 3.5 ± 0.7     | 11.4 ± 1.0    |
| Pyruvate (mg/dl)    | 0.6 ± 0.1     | 0.34 ± 0.06   | 0.7 ± 0.3     |
| Lactate (mg/dl)     | 18.3 ± 3.8    | 7.9 ± 1.3     | 13.7 ± 1.6    |
| Free fatty acid (mmol/l) | 1.92 ± 0.18 | 0.74 ± 0.09  | 1.83 ± 0.23   |
| Free insulin (µU/ml) | 4.17 ± 1.82  | ND             | 6.66 ± 1.76   |
| C-peptide (pmol/ml) | 0.08 ± 0.07   | ND             | 0.14 ± 0.1    |
| Cortisol (µg/dl)    | 72 ± 12       | 27.1 ± 1.7    | 54 ± 11       |

Data are means ± SEM. *P < 0.05, compared with the other groups. ND, not done.
arrival at the CRC. Random assignment was not based on sex or ethnicity. Because a priming dose of insulin adds an additional risk of hypokalemia, potassium levels were assessed and corrected on an hourly basis for the first few hours of therapy until glucose reached the predetermined goal of <250 mg/dl (i.e., ~4 h) and every 2 h thereafter.

**Laboratory procedures**

Laboratory studies included complete blood cell count, blood gas measurements, and routine blood chemistry values measured by standard assays in the clinical chemistry laboratory. In addition, plasma free insulin, C-peptide, β-hydroxybutyrate, acetocacetate, pyruvate, lactate, cortisol, and FFAs were assayed. Glucose was measured by a glucose oxidase method using a Beckman glucose analyzer. Plasma free insulin and C-peptide were measured after polyethylene glycol precipitation by a double-antibody radioimmunoassay method (14). Cortisol, FFAs, and ketone bodies were determined by previously described methods (2,15).

**Data analysis**

Overall mean comparisons for means and slopes for the three groups (load, no load, and twice no load) were made with one-way ANOVA using the Clinfo and SAS (SAS Institute, Cary, NC) software packages. These were followed by pairwise comparisons of averages and regression estimates of the slopes by observing the overlap/nonoverlap of the 95% confidence limits for all of the estimates (means and slopes). If any 95% confidence limits for an estimate overlapped, then no statistical significance was declared at \(P = 0.05\). If there was no overlap due to variability, then statistical significance was declared at \(P < 0.05\). This significance and nonsignificance is denoted by superscript letters (as in Table 4). Thus, groups having superscripts in common are not significant at \(P = 0.05\), whereas those having no superscripts in common are significant at \(P < 0.05\).

**RESULTS**

**Demographic and initial clinical data**

Table 1 shows the baseline characteristics of patients in the three treatment groups, with the following findings: 1) none of the patients were obese, 2) the majority of the patients were African Americans and were receiving insulin therapy, 3) omission of insulin (47%) and infection (33%) were the major precipitating factors for DKA, and 4) within the load group there were twice as many men as women, within the no load group there were three times as many women as men, and within the twice no load group men and women were equally distributed. However, in all of these groups, the majority of subjects were African American.

**Biochemical data on admission and after recovery**

Table 2 shows biochemical data on admission and at complete recovery from...
DKA in the three groups. Although there were no statistically significant differences among any of the parameters in the groups on admission, cortisol values are lower in the no load group than in the other two groups. It is of interest that all the subjects in this group are African Americans, the majority are women, and the free insulin level in this group is also lower in the no load group than in the other two groups. However, this counter-regulatory hormone, similar to that in previous reports (5,16,17), is still twofold higher than the baseline value. All measured parameters reached their near-normal values at recovery, with total ketone bodies reaching ~3.5 mmol/l. Of interest was the FFA level, which at recovery was about twice the normal value but consistent with elevated levels of FFA in diabetic patients without DKA (16). The mean anion gap at recovery was <12.

Figure 1 demonstrates the kinetics of intravenous insulin after infusion in the three arms. This figure shows that infusion of insulin of 0.07 (no load) or 0.14 unit·kg⁻¹·h⁻¹ (twice no load) without an initial bolus resulted in peaks of 66 and 202 μU/ml, respectively, whereas the use of an intravenous bolus of 0.07 unit/kg followed by a 0.07 unit·kg⁻¹·h⁻¹ infusion resulted in peak insulin of ~460 μU/ml at 5 min, which reached a plateau level of ~86 μU/ml in 30 min. It is also of interest that plateau levels of insulin for both the load and no load groups are not significantly different from 60 to 120 min. However, the twice no load group (0.14 unit·kg⁻¹·h⁻¹, which is ~10 units/h of insulin in a 70-kg patient) maintained higher levels of insulin during 30–120 min of infusion than those of the load or no load group.

Effect of various doses of insulin on recovery parameters
Table 3 demonstrates the outcome recovery data for DKA, depicting the time that predetermined values were reached for glucose, HCO₃⁻, and pH. The results suggested no significant differences in these values for the three doses of insulin, but 5 of 12 patients in the no load group required additional insulin for control of their blood glucose. The length of hospitalization was not significantly different among the groups, there were no complications in any of the groups, and no deaths occurred in this cohort. No hypokalemia was noted in any treatment group. The potassium nadirs were 4.3, 4.2, and 3.7 mEq/l in the load, no load, and twice no load groups, respectively (Fig. 2).

Table 4 shows estimates of the slopes for glucose, venous pH, ketones, FFAs, bicarbonate, and cortisol during the first 8 h of therapy in the three insulin therapy groups. The response of serum bicarbonate and cortisol showed no differences among the treatment groups. However, the slopes for glucose, venous pH, ketones, and FFAs varied among treatment groups.

**CONCLUSIONS**—Although numerous studies have effectively used low-dose insulin in the treatment of DKA (3,9,18), there are no data from a pro-

*Table 4—Slope estimates for clinical and hormonal responses to therapy over the first 8 h*

| Parameter                | Load group                      | No load group                    | Twice no load group               |
|--------------------------|---------------------------------|----------------------------------|-----------------------------------|
| Glucose (mg/dl)          | Initial value* 578.1 ± 63.7     | Estimate of slope 86.49*         | Initial value* 459.2 ± 38.2       | Estimate of slope 52.22*         |
| Venous pH                | 7.1 ± 0.03                      | 0.029±h                        | 7.13 ± 0.03                       | 0.025*                          |
| Ketones (mmol/l)         | 12.98 ± 1.14                    | −1.92*                          | 10.33 ± 1.3                       | −0.93b                          |
| FFAs (mmol/l)            | 1.92 ± 0.18                     | 0.34a                          | 1.83 ± 0.23                       | −0.21b                          |
| Serum bicarbonate (mEq/l)| 6.7 ± 0.7                       | 0.863a                         | 5.9 ± 0.8                         | 0.551a                          |
| Cortisol (μg/dl)         | 71.8 ± 11.7                     | −7.09a                         | 54.3 ± 10.5                       | −4.40a                          |

Data are means ± SEM. *No significant differences noted in initial values. †In comparisons involving load, no load, and twice no load treatment groups, those slope estimates with the same superscript are not significantly different at P = 0.05.
spective randomized study evaluating an insulin bolus (0.07 U/kg) compared with no bolus in conjunction with an infusion of low-dose insulin (0.07 vs. 0.14 unit·kg⁻¹·h⁻¹). Previous studies have demonstrated that although 0.1 unit/h of insulin in patients with DKA can effectively suppress hepatic gluconeogenesis by 50% (11).

We had previously shown that an intermediate dose of insulin of 0.1 unit·kg⁻¹·h⁻¹ (equivalent of 7 units/h of insulin in a 70-kg patient) by intravenous infusion was much more effective than a dose by the subcutaneous or intramuscular route (4). In these studies we used a priming dose. In addition, in a selected case report we have used as little as 6 units/h for a patient with modest DKA with further maintenance of euglycemia by 1–2 units/h (14). However, a bolus dose of insulin preceded the low-dose infusion (19). Furthermore, a priming dose has not been used for pediatric patients with DKA (10) and has not been recommended in the pediatric age-group in the latest ADA consensus report (12). Deleterious outcomes with the use of bolus insulin in this group may include hypokalemia as well as possible cerebral edema (12).

In summary, our study suggests that the use of a bolus or priming dose of insulin is not necessary when an adequate continuous insulin infusion such as 0.14 unit·kg⁻¹·h⁻¹ (or 10 units/h in a 70-kg patient) is used. However, a dose of 0.07 unit·kg⁻¹·h⁻¹ without priming is not adequate to obtain desired changes in glucose without supplemental doses of insulin.

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