Hypokalemia during Treatment of Diabetic Ketoacidosis: Clinical Evidence for an Aldosterone-Like Action of Insulin

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Objectives To investigate whether the development of hypokalemia in patients with diabetic ketoacidosis (DKA) treated in the pediatric critical care unit (PCCU) could be caused by increased potassium (K^+) excretion and its association with insulin treatment.

Study design In this prospective observational study of patients with DKA admitted to the PCCU, blood and timed urine samples were collected for measurement of sodium (Na^+), K^+, and creatinine concentrations and for calculations of Na^+ and K^+ balances. K^+ excretion rate was expressed as urine K^+-to-creatinine ratio and fractional excretion of K^+.

Results Of 31 patients, 25 (81%) developed hypokalemia (plasma K^+ concentration <3.5 mmol/L) in the PCCU at a median time of 24 hours after therapy began. At nadir plasma K^+ concentration, urine K^+-to-creatinine ratio and fractional excretion of K^+ were greater in patients who developed hypokalemia compared with those without hypokalemia (19.8 vs 6.7, $P = .04$; and 31.3% vs 9.4%, $P = .004$, respectively). Patients in the hypokalemia group received a continuous infusion of intravenous insulin for a longer time (36.5 vs 20 hours, $P = .015$) and greater amount of Na^+ (19.4 vs 12.8 mmol/kg, $P = .02$). At peak kaliuresis, insulin dose was higher in the hypokalemia group (median 0.07, range 0-0.24 vs median 0.025, range 0-0.05 IU/kg; $P = .01$), and there was a significant correlation between K^+ and Na^+ excretion ($r = 0.67$, $P < .0001$).

Conclusions Hypokalemia was a delayed complication of DKA treatment in the PCCU, associated with high K^+ and Na^+ excretion rates and a prolonged infusion of high doses of insulin. *(J Pediatr 2013;163:207-12)*.

Diabetic ketoacidosis (DKA) is the main cause of morbidity and mortality in young patients with diabetes mellitus.[1-3] Cerebral edema is the major cause of mortality occurring early during the therapy of children and adolescents with DKA, whereas hypokalemia may be an important cause for the late mortality.[4-6] In a retrospective chart review of 30 patients with DKA with a severe degree of hyperglycemia (initial plasma glucose concentration [$P_{Glucose}$] >50 mmol/L [900 mg/dL]) admitted to the pediatric critical care unit (PCCU) over a 6-year period,[7] we noted that 24 (80%) patients developed hypokalemia during their PCCU stay. Although this could be caused by a shift of potassium (K^+) into cells due to actions of insulin,[8] it seemed to be unlikely owing to the timing (the insulin infusion was started >24 hours earlier and there was a steady state with respect to the $P_{Glucose}$ for >12 hours). Accordingly, we performed a pilot study in 4 patients in whom urine electrolytes and creatinine were measured in each urine sample, and in every patient there was a high rate of excretion of K^+ while hypokalemia was present. There is evidence that insulin increases the activity of the epithelial sodium channel (ENaC) in the distal nephron and may have a kaliuretic effect.[9-12] Thus, the aim of this study was to prospectively investigate whether the development of hypokalemia in a population of patients with DKA treated in the PCCU could be caused by an increased urinary K^+ excretion and its association with insulin treatment.

Methods

This is a prospective observational cohort study of children and adolescents with DKA admitted to the PCCU of the Hospital for Sick Children, Toronto, Canada, from January 2007 to August 2008. The study was approved by the institutional research ethics board. Written informed consent was obtained from the patients' parents, and informed assent was obtained from the patients when appropriate. All patients admitted to the PCCU with DKA, defined by a $P_{Glucose}$ >11 mmol/L

ATPase	Adenosine triphophastase	P_K	Plasma potassium concentration
DKA	Diabetic ketoacidosis		
ENaC	Epithelial sodium channel	ROMK	Renal outer medullary K^+
IV	Intravenous	$U_{Creatinine}$	Urine creatinine concentration
K^+	Potassium	U_K	Urine potassium concentration
Na^+	Sodium	U_{Na}	Urine sodium concentration
PCCU	Pediatric critical care unit	U_{Na+K}	Urine sodium plus potassium
$P_{Glucose}$	Plasma glucose concentration		

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(200 mg/dL) with a venous pH <7.30 and/or a plasma bicarbonate concentration <15 mmol/L[1] were eligible for the study. The exclusion criteria were the administration of exogenous catecholamines that could lead to a shift of K^+ into cells or refusal to participate. Patients were treated according to the consensus guidelines.[1] Data collection included demographic and hemodynamic measurements, medications, and all input and output values (including those at the referral hospitals and during transport). Blood and timed urine samples were collected at 4-hour intervals for measurement of concentrations of sodium (Na^+), K^+, and creatinine. Balances of Na^+ and K^+ (in mmol/kg/d) were calculated by subtracting the amounts excreted in urine from all inputs via parenteral and enteral routes. The excretion of Na^+ was assessed using the ratio of the concentrations of Na^+ and creatinine in urine (urine sodium concentration (U_{Na})/urine creatinine concentration ($U_{Creatinine}$), expressed as mmol Na^+/mmol creatinine).[8] The excretion of K^+ was evaluated using the ratio of the concentrations of K^+ and creatinine in urine (urine potassium concentration (U_K)/$U_{Creatinine}$), which indicates overall renal response to K^+ disorders, and the fractional excretion of K^+, which relates the amount of K^+ excreted to the amount filtered. $U_K/U_{Creatinine}$ was expressed as mmol K^+/mmol creatinine, and the fractional excretion of K^+, expressed in percent, was calculated as follows[13,14]:

$$[(U_K/P_K)/(U_{Creatinine}/P_{Creatinine})] \times 100\ (\%)$$

The ratio of the concentrations of (Na^+ + K^+) and creatinine in urine (urine sodium plus potassium (U_{Na+K})/$U_{Creatinine}$), which reflects the number of effective osmoles that reaches the terminal cortical collecting duct, was expressed as mmol (Na^+ + K^+)/mmol creatinine.

Statistical Analyses

Analysis was made using GraphPad Prism version 5.0 (San Diego, California). Data were expressed as median (range). Patients were grouped according to the presence or absence of hypokalemia during PCCU stay. Continuous variables between groups were compared by use of Student *t* test or Mann-Whitney *U* test according to data distribution, and categorical variables were compared by use of Fisher exact test. Association between variables was assessed by use of Spearman correlation test. A value of $P < .05$ was considered significant.

Results

Thirty-four patients with DKA were admitted to the PCCU of the Hospital for Sick Children over the study period; 31 patients were included in the study. One patient was excluded because he was admitted to the PCCU with septic shock and received dopamine and epinephrine, and 2 patients were excluded because consent was not obtained. Patients' age ranged from 0.8 to 17 years (median 12 years), and their weight ranged from 8 to 100 kg (median 42 kg). There were 10 (32%) male patients, and 21 (68%) were newly diagnosed with diabetes mellitus. Twenty-nine (94%) patients had type 1 diabetes mellitus.

Twenty-five (81%) patients developed hypokalemia in the PCCU, and 6 (19%) did not have hypokalemia during PCCU stay. **Table I** (available at www.jpeds.com) shows demographic data and initial laboratory values in both groups; there was no significant difference in demographic data between groups. Patients who developed hypokalemia had a significantly lower plasma potassium concentration (P_K) and a lower pH at presentation compared with patients who did not develop hypokalemia during PCCU stay.

In the hypokalemia group, nadir P_K (median 3; range 2.2-3.4 mmol/L) occurred at a median time of 24 hours (range 14-50 hours) after therapy began. In the nonhypokalemia group, nadir P_K (median 3.7; range 3.6-4.4 mmol/L) occurred at a median time of 26.5 hours (range 10-31 hours) after initiation of therapy. Timing of nadir P_K was not significantly different between groups ($P = 1$). The median decrease in P_K (ie, the difference between initial values and nadir values of P_K) was 1.6 mmol/L (range 0.1 to 2.8 mmol/L) in the hypokalemia group and 2 mmol/L (range 1.2 to 3.2 mmol/L) in the nonhypokalemia group ($P = .15$) (**Figure 1**). Three patients in the hypokalemia group versus none in the nonhypokalemia group received sodium bicarbonate over the first 3 hours of treatment ($P = 1$).

Table II (available at www.jpeds.com) shows comparisons between groups at the time of nadir P_K. $U_K/U_{Creatinine}$, fractional excretion of K^+, $U_{Na}/U_{Creatinine}$, and $U_{Na+K}/U_{Creatinine}$ were significantly greater in patients who developed hypokalemia compared with those who did not have hypokalemia in the PCCU. Insulin dose administered via the intravenous (IV) route was significantly higher at nadir P_K in patients who developed hypokalemia, and they received a continuous IV insulin infusion for a longer period of time than did those who did not develop hypokalemia.

Peak values of $U_K/U_{Creatinine}$ were not significantly different in the 2 groups (median 33.3, range 10.5-107 vs median

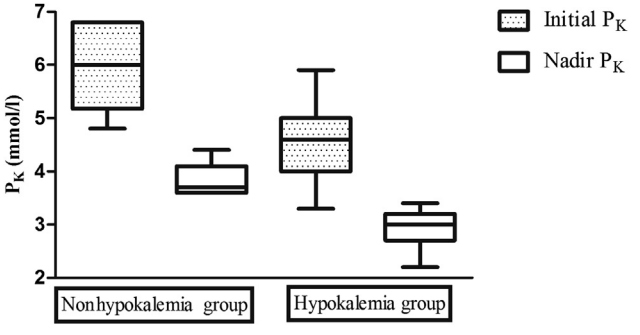

Figure 1. Initial and nadir values of P_K in hypokalemia and nonhypokalemia groups. *Central lines* are medians, *boxes* are IQRs, and *whiskers* indicate total range.