Hypocalcemia, Hypomagnesemia, and Transient Hypoparathyroidism During Therapy with Potassium Phosphate in Diabetic Ketoacidosis

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The effects of intravenous administration of potassium phosphate in the treatment of diabetic ketoacidosis were studied in nine children, ages 9 9/12 to 17 10/12 yr. During phosphate infusion (20–40 meq/L of fluid), all children maintained normal serum concentrations of phosphorus. Transient hypocalcemia occurred in six and transient hypomagnesemia in five patients. One child developed carpopedal spasms refractory to intravenous infusion of calcium gluconate but responsive to intramuscular injection of magnesium sulfate. In three patients, serum levels of intact parathyroid hormone were low at the time of hypocalcemia, an observation that suggests transient hypoparathyroidism. This study indicates that the use of potassium phosphate as the sole source of potassium replacement might potentiate ketoacidosis-induced hypocalcemia through multiple mechanisms. DIABETES CARE 2: 265–268, MAY–JUNE 1979.

Phosphorus depletion occurring during diabetic ketoacidosis is a well-known phenomenon and can be associated with compromised myocardial performance and depressed red cell oxygen delivery.[1–3] For these reasons, recent reviews have suggested the use of neutral potassium phosphate salts instead of potassium chloride as the preferred means of potassium replacement during fluid and electrolyte therapy for the acidotic dehydrated patient.[4,5] Following this mode of therapy, we have observed a diabetic ketoacidotic child (C.S.) with severe hypokalemia develop hypocalcemic tetany that was refractory to intravenous calcium gluconate but was responsive to magnesium sulfate. To determine the effects of potassium phosphate therapy on calcium and magnesium homeostasis, eight additional children with ketoacidosis were studied.

MATERIALS AND METHODS

The index case, patient C.S., was admitted for treatment of diabetic ketoacidosis that had been progressive for 48 h. Dehydration was estimated to be 7%. On admission, laboratory studies revealed a serum calcium of 8.3 mg/dl (Table 1), serum sodium of 130 meq/L, and serum potassium of 4.0 meq/L. The patient was given 600 ml of normal saline i.v. during the first 90 min, followed by half-normal saline at an initial rate of 250 ml/h. Each liter of fluid contained 40 meq neutral potassium phosphate during the initial 6 h of therapy. Regular insulin, 0.5 U/kg body weight, was administered; one-half i.v. and one-half s.c. on admission. During the next 36 h, she received an additional 45 U of regular insulin s.c. Acidosis and hyperglycemia were brought under control within 12 h, but hypokalemia developed (serum potassium 2.5 meq/L), requiring a marked increase in the rate of potassium salt infusion. 30 h after admission, the patient developed severe carpopedal spasm. At this time, serum calcium and phosphorus concentrations were 4.5 and 9.5 mg/dl, respectively. The symptoms were not alleviated by stopping the phosphate infusion and administering 10 ml of 10% calcium gluconate i.v. over 10 min. Magnesium sulfate, 2.2 ml of a 50% solution, was given i.m. Clinical improvement occurred during the next 15 min. Repeat determinations of calcium, phosphorus, and magnesium 24 and 48 h later were normal and have remained so since discharge.

During the ensuing 12 months, patients admitted to the general wards at the C. S. Mott Children's Hospital at the University of Michigan for treatment of diabetic ketoacidosis were placed on a standard protocol under the supervision of the Pediatric Endocrinology Service after obtaining informed consent from each patient's parent. There were four boys and three girls in addition to the index case. One girl (S.S.) was admitted on two separate occasions (a and b) during the study period. Ages ranged

TABLE 1
Calcium, magnesium, and pH values at time of admission, and the lowest Ca^{2+} and Mg^{2+} concentrations recorded during therapy

	Admission			Nadir during treatment			
Patient	pH	Ca^{2+} (mg/dl)	Mg^{2+} (mg/dl)	Ca^{2+} (mg/dl)	Hour	Mg^{2+} (mg/dl)	Hour
C.S.	7.01	8.3	—	4.5	30	0.6	30
S.S.$_a$	7.12	10.8	1.8	9.2	18	1.4	6
S.S.$_b$	7.05	10.6	1.9	8.6	24	1.3	12
J.M.	6.85	8.7	1.8	6.3	36	1.3	12
J.B.	6.92	9.2	—	8.6	4	—	—
S.V.	7.13	10.0	—	9.0	12	1.5	12
W.D.	7.16	11.3	1.9	10.4	24	1.6	12
J.E.	7.30	9.4	1.5	7.6	18	1.5	6
S.A.	6.92	9.3	1.8	8.7	12	1.4	12
Normal		8.8–10.9	1.5–2.7				

from 9 9/12 to 17 10/12 yr. Each patient received 10 to 20 ml/kg body weight of 0.9% saline for volume expansion during the first hour. Subsequent fluids consisted of 0.45% saline infused at an appropriate rate according to the estimated degree of dehydration and concurrent losses. Neutral potassium phosphate salts (20 to 60 meq/L of fluid) were provided during the recovery phase, and the potassium phosphate salt concentration was adjusted to maintain serum potassium concentration above 4.0 meq/L. In most cases, this was achieved with 40 meq/L. Two patients (J.E. and J.M.) inadvertantly received potassium chloride instead of phosphate between the 1 to 6-h and the 6- to 12-h periods of therapy, respectively. Regular insulin was administered separately with an infusion pump at a rate of 0.1 U/kg/h and was decreased to 0.05 U/kg/h after correction of acidosis (pH $\geq$ 7.30). Glucose (5%) was added to the i.v. fluids when capillary blood glucose concentration decreased to 250 mg/dl or less, as determined by hourly glucose determinations (Dextrostix). Patients with initial arterial blood pH values of $\leq$7.10 received sodium bicarbonate (2 meq/kg) during the first hour of therapy.

Serum concentrations of glucose, calcium (Ca^{2+}), magnesium (Mg^{2+}), inorganic phosphorus (P), and venous pH were determined at 6-h intervals by standard laboratory methods. Serum specimens for measurement of intact parathyroid hormone (PTH) concentrations were obtained at 6- to 12-h intervals during the first 72 h of treatment in five cases. Serum PTH concentrations were determined by radioimmunoassay by Laboratory Procedures (Kalamazoo, Michigan) as previously described.[6] The antiserum used in this assay has specificity predominantly for the intact PTH molecule (9500 mol. wt.), which is the principally secreted, but more rapidly cleared, form of PTH.

RESULTS

On admission, estimates of the degree of dehydration made by clinical appearance and measured weight loss ranged from 3 to 15% and did not correlate with the occurrence of hypocalcemia or hypomagnesemia. Serum glucose concentrations ranged from 300 to 657 mg/dl and showed no correlation with degree of acidosis, dehydration, or occurrence of hypocalcemia or hypomagnesemia.

Table 1 depicts the chemical profile of each patient at the time of admission, and nadir of Ca^{2+} and Mg^{2+} concentrations during treatment. At the time of admission, two patients (C.S. and J.E.) were marginally hypocalcemic, and J.E. was also hypomagnesemic and hypophosphatemic. This patient had received 2 L of 0.45% NaCl and 80 meq potassium chloride during the 12 h before being transferred to our care. Hypocalcemia occurred in six patients and was associated with tetany in C.S. The mean fall in Ca^{2+} was 1.6 mg/dl. The three patients with the lowest Ca^{2+} values on admission (C.S., J.M., and J.B.) subsequently had the lowest Ca^{2+} concentrations observed during treatment. Hypomagnesemia was documented in five patients, occurring simultaneously with hypocalcemia in two, and preceding hypocalcemia in the other three. The mean fall in Mg^{2+} was 0.5 mg/dl.

Serum P concentrations remained at or above admission values in all patients while receiving intravenous phosphate. Two patients (J.M. and J.E.) had a transient fall in their serum P concentrations (1.0 and 1.6 mg/dl) when they inadvertantly received potassium chloride instead of potassium phosphate for 6 h. Two other patients (C.S. and J.B.) had very high serum P concentrations on at least one occasion during recovery (9.5 and 6.9 mg/dl). The two children with the lowest recorded serum Ca^{2+} concentrations (C.S. and J.M.) had received the greatest amount of potassium phosphate salts (11.1 and 11.3 meq/kg/24 h). The average amount of potassium given to all patients during the first 24 h of therapy was 5.0 $\pm$ 1.24 meq ($\bar{x}$ $\pm$ SE) per kg body weight.

Three children who had transient hypocalcemia on at least one occasion had sequential determinations of serum PTH

during treatment. In all three cases, PTH values were low for the corresponding Ca^{2+} concentration and in the range observed in patients who have proven hypoparathyroidism (Figure 1). Sequential PTH determinations in two children who did not experience hypocalcemia were normal.

DISCUSSION

There has been renewed interest in the administration of phosphate to children being treated for diabetic ketoacidosis, and it has been suggested that appropriate phosphate replacement can be accomplished by using neutral potassium phosphate salts as the sole source of potassium replacement.[4,5,7] The use of phosphate as an essential part of replacement therapy was advocated in the late 1930s because of the observed fall in serum P concentration and the theoretical requirement of P in the glycolytic pathway.[4] Recently, others have suggested that phosphate administration might help repair depleted red cell levels of 2,3-diphosphoglycerate (2,3-DPG), thus facilitating oxygen delivery[1,2] and preventing the depressed myocardial contractility observed in the hypophosphatemic state.[3] Previous investigators have reported a P deficit averaging 3 meq/kg body weight in adults with ketoacidosis.[8,9] Lightner et al.[7] have demonstrated that in children, potassium replacement with the chloride salt is associated with a significant fall in serum P concentration, whereas no decrement occurred when potassium phosphate was used for potassium replacement (40 meq/L of fluid). A similar pattern was seen in the present study.

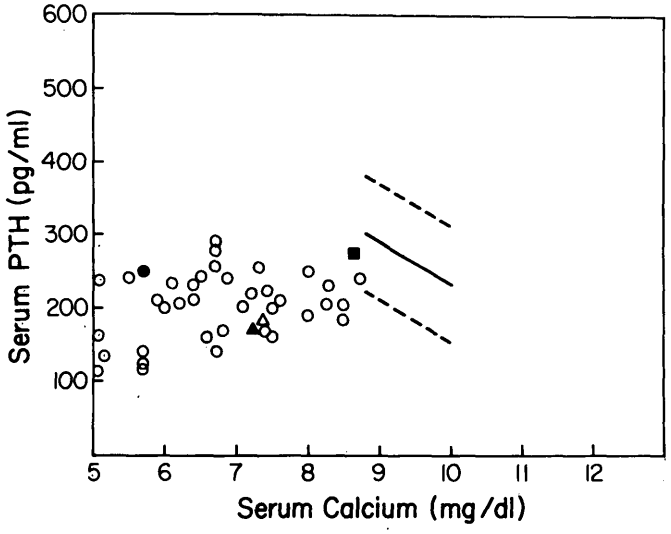

FIG. 1. Serum intact PTH concentrations as a function of serum calcium concentrations in patients C.S. (● 32 h), J.E. (△ 12 h, ▲ 24 h), and S.A. (■ 12 h). Open circles (○) are the points for 37 patients with surgical or idiopathic hypoparathyroidism. Normal mean ± 2 SD is indicated by the solid (—) and broken (– – –) lines, respectively. (This figure was adapted from Fig. 6, ref. 6.)

Tetany following therapy for ketoacidosis is an unusual finding in spite of the well-documented depletion of both Ca^{2+} and Mg^{2+} which occurs during the polyuric phase of hyperglycemia and acidosis.[8–10] Significant Ca^{2+} and Mg^{2+} losses have been demonstrated during acidosis and the first hours of recovery. Atchely et al.[10] demonstrated that negative Ca^{2+} balance occurs immediately following insulin withdrawal, progresses with acidosis, and continues through the first few days of recovery. Martin et al.[9] measured serum and urine Ca^{2+} and Mg^{2+} concentrations in 29 patients with ketoacidosis and found that 28% were hypocalcemic and 7% were hypomagnesemic when first seen. Balance studies demonstrated that with standard treatment, large amounts of both Ca^{2+} and Mg^{2+} continued to be lost through the urine. After 12 h of therapy, 73% of the patients were hypocalcemic, and 55% were hypomagnesemic. Since hypocalcemic states are associated with defective pancreatic β-cell insulin release,[11] it is possible that the impairment of residual insulin secretion that occurs after ketoacidosis is in part secondary to prolonged negative Ca^{2+} balance.

In the present report, hypocalcemia occurred 12–30 h after institution of therapy in five of nine patients, when their serum pH was normal. Hypocalcemic tetany occurred in one patient who received a large amount of phosphate because of severe hypokalemia. This resulted in hyperphosphatemia and probably contributed directly to the marked degree of hypocalcemia and possibly to hypomagnesemia.[12] Hypomagnesemia was present in five of nine patients in this study and was temporally associated with hypocalcemia in two patients.

The etiology of Ca^{2+} and Mg^{2+} loss is thought to be osmotic diuresis and the increased mobilization from bone of both ions induced by acidosis.[8,13] However, other mechanisms might be involved also. Glycosuria, without acidosis, has been shown to triple urinary Ca^{2+} excretion and double urinary Mg^{2+} loss.[14] Acidosis might also inhibit renal tubular reabsorption of Ca^{2+} ions, leading to further urinary losses.[15] Administration of insulin, 0.1 U/kg, has been shown to cause small increases in urinary Mg^{2+} excretion.[16]

Magnesium metabolism is also affected by aldosterone. Christlieb et al.[17] have shown increased levels of this hormone during ketoacidosis as a consequence of hypovolemia. Increased serum concentrations of aldosterone have been associated with, and thought to cause, the Mg^{2+} depletion of primary and secondary hyperaldosteronism[18,19] and may contribute to the hypomagnesemia of diabetic ketoacidosis.

When Mg^{2+} depletion becomes severe, a reversible state of hypoparathyroidism can occur. Hypomagnesemia appears to inhibit both synthesis and release of PTH and also decreases peripheral responsiveness to PTH.[20,21] This state of hypoparathyroidism would abolish the homeostatic

Ca^{2+} control mechanisms that normally maintain serum Ca^{2+} concentrations despite continued losses. Three patients in our study had evidence of impaired parathyroid responsiveness. When serum Ca^{2+} concentrations were lowered to a similar degree (2 mg/dl below base line) by EDTA infusion in 10 adult volunteers, the mean serum PTH concentration with this assay increased 200% within 2 h (C. D. Hawker and R. D. Utiger, unpublished observations). The impaired PTH responsiveness in our patients might have been a result of Mg^{2+} depletion. The lack of response to intravenous Ca^{2+} administration in patient C.S. and the improvement of carpopedal spasm after administration of Mg^{2+} sulfate would support this hypothesis.

In summary, the use of potassium phosphate salts for replacement of potassium can maintain serum P concentrations at or above normal values and seems reasonable in light of the known functions of P in maintaining red cell concentrations of 2,3-DPG and myocardial function. However, in view of the well-established tendency toward hypocalcemia and hypomagnesemia in diabetic ketoacidosis, and the suppressive effect of increased serum P on Ca^{2+} concentration, administration of potassium solely in the form of its phosphate salts may make it more difficult to maintain normal potassium concentrations without causing hypocalcemia.

Although a control group was not studied, the data presented here confirm the periodic occurrence of decreased serum Mg^{2+} and Ca^{2+} when this therapeutic program is used and document the possibility of transient hypoparathyroidism. Recently, we have advocated the use of an equal mixture of potassium chloride and neutral phosphate (20 meq of each per liter of i.v. fluid). The complications described above have not been observed with this program.

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