Thiazides and hypokalaemia in diabetic ketoacidosis

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Summary

In a series of forty-one episodes of diabetic coma or pre-coma, three patients had plasma potassium values of less than 3.0 mEq/l. All three had been taking thiazide diuretics with only one receiving oral potassium supplements. None was previously known to be diabetic, representing 18% of the new diabetics in the series. The mean plasma potassium for the other new diabetics was 4.7 ± 0.2 mEq/l. These findings emphasize that adequate potassium supplements should be given with thiazide diuretics to diabetic subjects and to those with an increased risk of developing the disease.

Introduction

Diabetic coma and pre-coma are still associated with a significant mortality, approximately 8% in series from general hospitals (Beigelman, 1971; Alberti & Hockaday, 1972). Precipitating factors include infection and deficient insulin dosage although in many subjects no precipitant can be found. Obviously, detection of avoidable factors is of value.

Potassium depletion can cause glucose intolerance (Sagild, Andersen & Andreasen, 1961). Thiazide diuretics may cause both potassium depletion and deterioration in glucose tolerance but their effects on normal subjects are controversial (Breckenridge *et al.*, 1967; Goldner, Zarowitz & Akgun, 1960; Rapoport & Hurd, 1964). However, studies in latent or mild diabetics clearly show deleterious effects of chlorothiazide on carbohydrate metabolism (Bojanowicz & Zubowski, 1967). It has been suggested that chlorthalidone and frusemide cause only mild potassium depletion with little or no effect upon glucose intolerance or insulin secretion (Healy *et al.*, 1970) although diabetes mellitus has been reported after chlorthalidone therapy (Andersen & Persson, 1968; Moret, 1965).

We present below case reports of three previously undiagnosed diabetics admitted with hypokalaemia and severe diabetic ketoacidosis all of whom were taking thiazide diuretics. These data are reported to emphasize, first, the need to pay particular notice to potassium therapy when thiazides are given to diabetics and those at risk of developing the disease and, second, the possible diabetogenic effect of these compounds.

Subjects

In the past 15 months thirty-eight patients have been admitted to this hospital with forty-one episodes of severe ketoacidosis, defined as uncontrolled diabetes of a severity necessitating urgent intravenous fluid, electrolyte and insulin therapy with total ketone bodies (acetoacetate plus 3-hydroxybutyrate) of more than 3 mEq/l. In seventeen (45%) of these patients diabetes had not previously been diagnosed. Only three had been taking thiazide diuretics, and only one was receiving any oral potassium supplement. One other of the new diabetics was also receiving a thiazide diuretic but presented with normal serum potassium, while only one of the twenty-one known diabetics was on chronic diuretic therapy.

Case 1

S.C. (R.I. No: 494544), a 52-year-old housewife, was admitted in diabetic 'coma'. Two months previously she had been prescribed Durophet (an amphetamine preparation) and chlorthalidone, 100 mg/day, as well as a reducing diet, because of obesity. At that time the presence of diabetes mellitus had not been detected. She lost 14 lb in weight during the 2 months but became thirsty and drank excessively after 1 month of treatment. The day before admission muscular weakness and lassitude developed, and she was drowsy and vomiting during the final 12 hr. There was no family history of diabetes nor past personal history of serious illness.

On admission she was dehydrated and ketotic with air hunger. Blood pressure was 105/60 mmHg. Some details of blood biochemistry and treatment are given in Table 1. Blood urea was 85 mg/100 ml. Because of the early knowledge of hypokalaemia bicarbonate was given cautiously, 60 mEq at 2 hr and again 3 hr after starting insulin. In the first $3\frac{1}{2}$ hr she received $2\frac{1}{2}$ l of 'normal' saline and was then changed to 0.54% saline.

She became normally conscious after 2 hr of treatment and indeed was excessively talkative until she fell asleep around the sixth hour. Next morning a right hemiparesis with dysphasia was present but these signs had greatly improved 1 month later when she was talking normally and could walk with assistance. She was still on insulin treatment.

TABLE 1. Biochemical findings and treatment

	Time after insulin commenced (hr)	Blood glucose (mg/100 ml)	Total ketone bodies (mEq/l)	pH	Plasma sodium (mEq/l)	Plasma potassium (mEq/l)	Cumulative insulin (units)	Cumulative potassium (mEq)	Cumulative i.v. potassium (mEq)
Case 1	0	1200	17.6	7.04	122	2.9	100	0	
	1	970	12.4	—	—	1.4	100	7	
	3	600	10.7	7.18	135	2.0	172	91	
	5	315	12.2	—	144	4.5	172	234	
	12	225	—	7.42	140	4.9	172	307	
Case 2	0	700	5.1	7.41	140	2.8	80	0	
	1	410	3.1	—	144	2.6	80	7	
	5	225	0.5	—	—	3.2	96	65	
	14	330	—	—	134	4.1	112	117	
	24	245	0.2	—	134	4.2	144	156	
Case 3	0	720	16.0	7.15	135	2.0	100	0	
	1	715	—	—	—	2.0	200	0	
	5	115	—	—	130	2.4	200	39	
	11	140	—	—	126	1.8	208	39	
	17	—	—	—	—	3.0	208	91	
	24	—	1.3	—	—	—	208	117	

Case 2

J.O. (R.I. No: 43431), a 65-year-old female, was admitted as an emergency in diabetic 'coma'. Mild hypertension had been found 6 years before, and for the last 6 months she had been treated with chlorthalidone 100 mg/day and methyldopa, 250 mg thrice daily. For some weeks she had noticed mild weight loss, with nocturia and polyuria for 3 weeks, thirst for 1 week, and vomiting for 2 days. There was no previous indication that she had diabetes.

On admission she was conscious with normal respiration and blood pressure 160/100, but markedly dehydrated. Again the essentials of biochemistry and treatment are shown in Table 1. Blood urea was 88 mg/100 ml. She was not given bicarbonate and after 2½ l of 'normal' saline in 6 hr the intravenous fluid was changed to 4% glucose in one-fifth 'normal' saline.

She made an uneventful recovery and remains on insulin treatment.

Case 3

K.R. (R.I. No: 361141), a 48-year-old female, was admitted with the complaints of loss of appetite, vomiting, thirst and polyuria for 1 week, with abdominal pain and nausea and drowsiness on the day of admission. She was not previously known to be diabetic and there was no family history of diabetes. Five months previously she had been investigated for vague malaise. The blood glucose was then normal, while an enlarged liver, atrophic gastritis, achlorhydria and a BSP retention of 16% were also discovered. She had been treated with diuretics for 2 years, and after her last admission she took bendrofluazide 25 mg b.d. and 'Slow K', Ciba, one tablet b.d. (potassium chloride, 0.6 g b.d.).

On admission she was dehydrated with marked air hunger and a palpable liver edge; pulse was 100/min and BP 120/80 mmHg. Blood values and treatment are summarized in Table 1. The 3-hydroxybutyrate/acetoacetate ratio was exceptionally high at 32 (corroborated by a negative Ketostix). Blood glucose fell to 115 mg/100 ml by 5 hr after treatment but plasma potassium was 1.8 mEq/l 10 hr after insulin and still only 2.9 mEq/l 4 days later. Difficulty was encountered with intravenous therapy, so that only mild potassium replacement was achieved (Table 1). After incision of a perianal abscess she made an uneventful recovery and was discharged on 32 units soluble insulin and 20 units isophane insulin per day.

Discussion

Severe hypokalaemia has been described in a minority of diabetics since this condition was first recognized (Abramson & Arky, 1966; Sheldon & Pyke, 1968), although it was a notable feature of the 'epidemic' of severe ketoacidosis reported in association with an influenza epidemic (Watkins *et al.*, 1970). In three recent series involving a total of 164 episodes no initial hypokalaemia was noted (Cohen *et al.*, 1960; Cryer & Daughaday, 1969; Malins, 1968) while Beigelman reported serum potassium values of less than 3.5 mEq/l in only 4% of a series of 327 cases (Beigelman, 1971). In a recent Californian series (twenty-five episodes of ketoacidosis) (Kiralý, Becker & Williams, 1970) the only patient who developed symptoms of hypokalaemia during treatment (serum potassium 1.6 mEq/l) had been on thiazides, and also had the lowest initial potassium concentration (3.3 mEq/l). Initial or severe hypokalaemia is of grave prognostic significance (Abramson & Arky, 1966; Watkins *et al.*, 1970; Holler, 1946).

The occurrence of hypokalaemia in three of seventeen newly diagnosed diabetics presenting with severe diabetic ketoacidosis is of significance when taken in conjunction with the fact that all three were taking thiazide diuretics, two without potassium supplementation. The initial mean plasma potassium in the other fourteen subjects was 4.7 ± 0.2 (SE) mEq/l with the three thiazide patients all more than 2 SD below this value. It is impossible to decide whether these subjects were mild undiagnosed diabetics or non-diabetics before thiazide therapy and whether the thiazide or the hypokalaemia precipitated the severe ketoacidosis. In favour of the thesis that these subjects were all potential diabetics is the finding that all required continued substantial insulin therapy even after correction of hypokalaemia and cessation of the thiazides. Vomiting before admission was not confined to these three, nor was it severe enough to cause this degree of hypokalaemia.

Severe ketoacidosis has infrequently been reported as a hazard of thiazide therapy (Sugar, 1961). More often transient hyperglycaemia occurs, though it is not rare for patients with hyperosmolar non-ketotic hyperglycaemia 'coma' to be receiving treatment with thiazides (Portier *et al.*, 1968; Solvsteen, Olsen & Hansen, 1968). It is of interest that 125 mg chlorthalidone/day with potassium supplementation caused significant hyperglycaemia in 91% of a series of non-diabetic mental patients, and they also showed reduced blood levels of insulin-like activity and reduced responsiveness of adipose tissue to insulin (Dobrzanski, 1969) although Nicole & Pulver found effects only in diabetic subjects but not in normal subjects (Nicole & Pulver, 1962).

However, potassium depletion is known to be present even in well controlled diabetics (Telfer, 1966). The danger of provoking further potassium loss emphasizes the need for prescription of adequate amounts of supplementary oral potassium to all who receive potassium-losing diuretics if these patients have the least likelihood of developing diabetes. Observations of potassium loss in healthy subjects may not apply to patients in the yet undiagnosed phases of a disease.

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