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Moduretic-induced metabolic acidosis and hyperkalaemia

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Summary

A patient who developed significant metabolic acidosis and severe hyperkalaemia while taking Moduretic (amiloride and hydrochlorothiazide) is reported. During the period of hyperkalaemia (maximum potassium 7·6 mmol/l) the patient's whole body potassium content was normal. His acid-base balance and serum potassium returned to normal some 10 days after stopping the drug. The possible mechanism of acidosis and hyperkalaemia in this patient is discussed.

Introduction

Although hyperkalaemia is a recognized complication of many potassium-sparing diuretics (Greenblatt and Koch-Weser, 1973; Neale, Lynn and Bailey, 1976; Bailey, 1978), the development of severe acidosis with these drugs in man has received far less attention. Recently 6 cirrhotic patients who developed reversible metabolic acidosis during treatment with spironolactone were described (Gabow, Moore and Schrier, 1979). A man is reported who developed significant metabolic acidosis whilst taking Moduretic (amiloride and hydrochlorthiazide). The authors further believe that this is the first patient who has had his whole body potassium measured while hyperkalaemic as a result of this drug.

Case report

In June 1978 an 80-year-old man was referred with a 2-month history of intermittent falling without apparent injury. The falls had started after discharge home following an uneventful transurethral prostatectomy for benign prostatic hypertrophy. There was a 17-year history of rheumatoid arthritis, the symptoms of which were controlled with indomethacin in a total daily dose of 150 mg. He had been taking one daily tablet of Moduretic (5 mg amiloride + 50 mg hydrochlorothiazide) for ankle oedema for one month.

Physical examination showed him to be pale but physically well built and mentally alert. He had signs of non-active rheumatoid disease with probable associated osteoarthritic changes affecting the hands, elbows, shoulders and knees. The cardiovascular system was essentially normal with a BP of 180/85 mmHg and no postural drop. Electrocardiogram showed flattened T-waves over the chest leads compatible with minor ischaemic changes. The serum electrolytes were normal although his renal function was impaired (Table 1: 27.6.78). His drugs were continued unchanged and a course of physiotherapy was prescribed.

One month later he reported considerable improvement in his mobility and said that he had had no further falls. After a further month (30.8.78) he was reviewed again and on this occasion was complaining of extreme tiredness. Physical examination was essentially unchanged. There was no evidence of significant muscle weakness. However, his serum electrolytes showed extreme hyperkalaemia and acidosis with an accompanying increase in renal failure (Table 1: 30.8.78). Arterial blood gas analysis confirmed that the acidosis was primarily metabolic and that there was some respiratory compensation. Blood lactate and pyruvate levels were normal. The ECG now showed positive deflection of T-waves over the chest leads, though these were not 'tented'. The whole body potassium was measured (31.8.78) in a shadow shield whole body counter by the ^{40}K method with ^{42}K calibration and the result (2490 mmol) was normal for a man of this age, height and weight. He was admitted from the clinic and given 10 units of soluble insulin on 2 occasions and the Moduretic was withdrawn. His metabolic acidosis gradually resolved over a period of 10 days. Repeat measurement of his whole body potassium when his serum potassium and blood gases had returned to normal (Table 1: 26.9.78), was unchanged at 2510 mmol. Clinically

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TABLE 1. Serial electrolytes and blood gas analyses

Date	27.6.78	30.8.78	31.8.78	4.9.78	11.9.78	26.9.78
Sodium (mmol/l)	136	135	133	132	138	137
Potassium (mmol/l)	4·8	7·6	7·6	5·3	4·8	4·3
Chloride (mmol/l)	103	111	112	102	111	100
Bicarbonate (mmol/l)	23	17	17	18	22	28
Urea (mmol/l)	16.1	20·9	20·0	16·4	14·3	12·6
Creatinine (mmol/l)	0·16	0·19	0·18	0·19	0·19	0·17
pH			7·25		7·32	7·38
Pa,CO_2 (kPa)			3·72		4·26	5·19
Base excess (mmol/l)			−12·8		−7·4	−0·8
Creatinine clearance (ml/min)				21·4		32·3

Conversion: SI to traditional units: urea: 1 mmol/l≈6 mg/100 ml; creatinine: 1 mmol/l=11·3 mg/100 ml; Pa,CO_2: 1 kPa ≈7·5 mmHg.

the patient improved and was discharged home on his initial therapy with the exception of the Moduretic.

Discussion

The risk of hyperkalaemia with potassium-sparing diuretics is well recognized (Greenblatt and Koch-Weser, 1973; Neale *et al.*, 1976). Spironolactone has been most frequently implicated and to a lesser extent, also triamterene and amiloride (Bailey, 1978). In one study (Neale *et al.*, 1976) spironolactone was found to aggravate renal function impairment in elderly patients; renal function is generally recognized as declining progressively with increasing age. In the present case the development of hyperkalaemia, metabolic acidosis and deterioration in renal function after 3 months' daily ingestion of Moduretic, and the return of the biochemical values to their previous levels some 10 days after the drug was discontinued strongly suggests that Moduretic was the aetiological agent.

An unusual feature of this patient was the development of a marked metabolic acidosis with high serum potassium unaccompanied by an increase in whole body potassium. The relatively minor degree of impairment of renal function could not be responsible for the marked metabolic acidosis and hyperkalaemia in this subject. Although amiloride is known to have an inhibiting effect on renal tubular hydrogen ion secretion, the action is thought to be slight (Goodman and Gilman, 1975). In general it is believed that when amiloride is combined with a thiazide, as in Moduretic, the natriuretic effect of the 2 drugs is additive and the amiloride antagonizes potassium excretion. Hyperkalaemia is thus likely to occur and this is especially so in patients with impaired renal function. However, the evidence in this case does not support this view. It would appear that amiloride had a profound action on renal hydrogen ion transport leading to metabolic acidosis. It did not increase the total amount of potassium in the body but the severe hyperkalaemia was probably due to a shift of potassium ion from inside the cells to the plasma. It is well known that this shift occurs in the presence of severe acidosis (Black, 1972). It is also possible that hyperkalaemia might in turn suppress renal ammonium excretion and accentuate the metabolic acidosis (Tannen, 1977). Since no study of whole body potassium in relation to potassium-sparing diuretics has been reported the mechanism by which these drugs cause hyperkalaemia merits further investigation.

One complicating factor in this case is the concurrent use of indomethacin, a potent prostaglandin synthesis inhibitor. It has recently been suggested that impaired renal prostaglandin production contributes to the pathogenesis of hyporeninaemic hypoaldosteronism (Norby *et al.*, 1978), which is characterized by acidosis and hyperkalaemia. The abnormalities are in direct contrast to those in Bartter's syndrome in which overproduction of renin and aldosterone is associated with severe hypokalaemia and alkalosis. Whether indomethacin, by inhibiting prostaglandin synthesis, contributed to the development of acidosis and hyperkalaemia in this patient is uncertain, but it is possible that Moduretic and indomethacin acted synergistically in this respect. However, the fact that the patient's biochemistry returned to normal when Moduretic was stopped whilst indomethacin was continued suggests that the diuretic played the dominant role in causing these abnormalities.

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