Hypokalaemia, Flaccid Quadruparesis, and Myoglobinuria with Carbenoxolone (Biogastrone)

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Carbenoxolone has recently been advocated (Doll *et al.*, 1962, 1965 ; Horwich and Galloway, 1965) for the treatment of chronic gastric ulcer. A number of side-effects have been encountered. Thus both Doll *et al.* and Horwich and Galloway noted salt and water retention and weight gain, with or without hypertension, in 20% and 31% of their patients respectively, and headache and heartburn were troublesome in a few of the cases.

There are conflicting reports in the literature on the salt-retaining and kaluretic properties of liquorice and its derivatives both in man and in experimental animals (Salassa *et al.*, 1962). A case is accordingly described of a middle-aged woman developing severe hypokalaemia in the absence of weight-gain, flaccid quadruparesis, and myoglobinuria after treatment with carbenoxolone in standard dosage over a period of 38 days.

Case Report

A 58-year-old housewife with dyspeptic symptoms and loss of weight for 10 weeks was found to have a large lesser-curve ulcer of the stomach. Radiological appearances did not allow the certain exclusion of malignancy. The erythrocyte sedimentation rate (E.S.R.) was 45 mm. in one hour ; normal results were obtained for the blood values, serum electrolytes, urea, proteins, and transaminases. Urinalysis was negative.

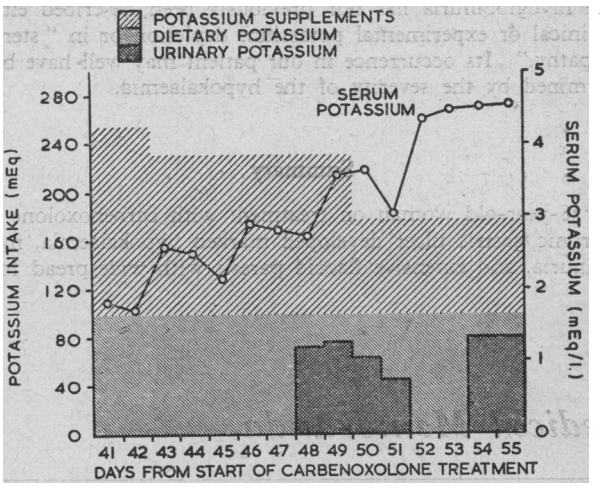
On 30 August 1965 (day 1) treatment was begun with bed rest, sedation with amylobarbitone, Gelusil (magnesium trisilicate and aluminium hydroxide) for symptomatic relief of pain, and carbenoxolone, 100 mg. three times daily. A close watch was kept on the body weight and the blood-pressure, but neither showed any significant change. The dyspeptic symptoms abated within a few days, and after 12 days she was transferred to a convalescent hospital to continue with the carbenoxolone treatment for a further three weeks.

On return to the ward on 1 October (day 33) she was still well and symptom-free. The E.S.R. had fallen to 16 mm. ; blood values remained normal. Urine showed no chemical or microscopical abnormality. Barium studies showed the ulcer to have healed completely.

On 6 October (day 38) she complained of vague muscular cramps in the limbs, and on the next day passed a dark-brown urine. The abnormal pigment was identified as myoglobin, the absorption maxima of the carboxy-derivative (Thompson and Broughton, 1961) being 542 and 572 mμ, as compared with 539 and 560 mμ for carboxyhaemoglobin. Over the next 48 hours she showed progressive flaccid paresis of all four limbs, the weakness predominantly affecting the proximal muscles of the limbs and the deep muscles of the back. The affected muscles were diffusely tender. The deep tendon reflexes were hypoactive, but the plantars were flexor and there was no other neurological abnormality.

Investigations.—Serum electrolytes (mEq/l.): sodium 132, potassium 1.8, chloride 90, CO_2 38 ; urea 16 mg./100 ml. ; marked hypokalaemic changes in the cardiogram with multiple ventricular ectopics ; serum glutamic oxaloacetic and pyruvic transaminases >220 and >125 Frankel units respectively ; urine negative for sugar and albumin ; urinary creatine 162 mg./24 hours ; formed elements of urine (Prescott and Brodie, 1964): renal tubular cells 1,691,000 per hour (normal <180,000), leucocytes 1,540,000 per hour (normal 500,000), red cells 50,000 per hour (normal). An electromyogram of the right biceps was silent at rest, but on maximal volition there was a characteristic interference pattern of myopathic type with a large number of high-frequency potentials of low voltage. Biopsy of the left deltoid showed focal necrosis of the muscle.

Carbenoxolone was stopped after the onset of myoglobinuria on the 39th day. Treatment was initially with parenteral potassium by drip infusion followed by effervescent potassium by mouth. Myoglobin gradually disappeared from the urine over 72 hours, and the serum electrolytes, particularly the potassium (see Chart), reverted to normal over the next 10 days. Improvement in strength of the muscles of the limbs ensued with the rise of the serum potassium, but full recovery did not occur for a further two weeks. By this time the serum transaminases had gradually reverted to normal and the formed elements of the urine assumed normal proportions.



Potassium balance after the onset of quadruparesis. (The dietary intake is assumed to be 100 mEq/day.)

Discussion

Hypokalaemic alkalosis and muscular paresis as a result of excessive ingestion of liquorice have been reported in a number of cases in the Continental literature (Mollaret *et al.*, 1960 ; Drosdowski *et al.*, 1961 ; Giroire *et al.*, 1961 ; Garcin *et al.*, 1961 ; Jenny *et al.*, 1961). In a similar patient Salassa *et al.* (1962) obtained correction of the hypokalaemic alkalosis with spironolactone. There was no detectable aldosterone in the urine, thus suggesting that liquorice itself had an aldosterone-like effect.

The electrolyte disturbance in our patient was primarily one of hypokalaemia of marked severity, and as the only other medication was with a barbiturate and Gelusil it seems reasonable to suppose that the carbenoxolone was responsible for this effect. Horwich and Galloway (1965) found a "slight fall" in serum potassium in patients on prolonged treatment with the drug. A rough estimate from the data in the Chart suggests that the potassium deficiency in the present case was of the

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order of 1,500 mEq—that is, more than half the total exchangeable body potassium. At no time was there any weight gain or elevation of the blood-pressure. Complete reliance on these two parameters is accordingly unwise, as severe hypokalaemia may occur in their absence, and prophylactic use of a thiazide (*B.M.J.*, 1964) to safeguard against the potential risks of fluid retention may only aggravate the problem.

Muscle weakness and wasting, sometimes progressing to muscle necrosis and a myopathy, are well recognized as occasional complications of corticosteroid therapy. The precise mechanism of muscle damage in these cases is obscure. Ellis (1956) noted an increase of sodium and depletion of potassium in the affected muscles of cortisone-treated rabbits, and a similar lesion could be induced by potassium depletion alone. Large doses of potassium, however, failed to prevent the lesion in cortisone-treated animals, and in the "steroid myopathy" in man, resulting from triamcinolone (R. S. Williams, 1959), dexamethasone (G. T. Williams, 1959; Golding and Begg, 1960), and fludrocortisone (Maclean and Schurr, 1959), hypokalaemia has been notably absent.

In the absence of a personal or family history of idiopathic paroxysmal myoglobinuria it would seem reasonable to suppose that the myoglobinuria was a result of the muscle necrosis, either from a primary "steroid-like" effect of the drug or from the severe potassium depletion. In experimental potassium deficiency vacuolar degeneration progressing to necrosis of the cardiac and skeletal muscles and the renal tubular epithelium has been described (Bland, 1956; Ellis, 1956). In the present case there was a quantitative increase of renal tubular cells and histological evidence of focal muscle necrosis. To our knowledge myoglobinuria has not previously been described either in clinical or experimental potassium depletion or in "steroid myopathy." Its occurrence in our patient may well have been determined by the severity of the hypokalaemia.

Summary

A 58-year-old woman on treatment with carbenoxolone for a chronic gastric ulcer developed marked hypokalaemia, myoglobinuria, and extensive flaccid paresis with widespread focal necrosis of the muscles. Complete recovery ensued after withdrawal of the drug and correction of the potassium deficit.

ADDENDUM.—Since this report was submitted A. G. G. Turpie and T. J. Thomson (*Gut*, 1965, **6**, 591) have recorded hypokalaemia (serum potassium below 3 mEq/l.) in four of 10 patients receiving carbenoxolone sodium 300 mg. daily, and in two of 10 patients on 150 mg. daily, for a maximum period of four weeks. E. G. Gross, J. D. Dexter, and R. G. Roth (*New Engl. J. Med.*, 1966, **274**, 602) have reported hypokalaemic myopathy with myoglobinuria in a 45-year-old housewife who had ingested 30 to 40 g. of liquorice daily and 50 mg. of hydrochlorothiazide three times a week for nine months for weight reduction.

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Medical Memoranda

Longitudinal Pigmentation of the Nails in Addison's Disease

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Melanin pigment is usually absent from the nails of white-skinned people. A patient is described who developed longitudinal bands of brown pigmentation in the finger-nails during the course of Addison's disease, and the implications of this are discussed.

CASE REPORT

(Hospital No. 213251.) A man aged 57 years was admitted for investigation on 24 June 1965. He complained of palpitations, tiredness, and leg cramps on exercise during the previous six months. Other symptoms were loss of 10 lb. (4.5 kg.) in weight, frequency of micturition, recent onset of Raynaud's phenomenon of the fingers, and impotence for nine months.

The patient had had quinsy in 1945 and December 1964. His family history showed that he was English with no known gipsy or foreign blood. Examination showed a thin but well-nourished man of 132 lb. (59.9 kg.), his skin being pigmented a deep brown all over, including the oral mucous membranes and the genitalia. On the trunk multiple darker spots were present.

The nails of his right thumb and left thumb, index, and ring fingers showed mahogany-brown longitudinal streaks running from the base of the nail to the cut edge; these had been present for six months, dating from his earliest symptoms (see Fig.). There was no pigmentation of the eyes or rectal mucosa. The pulse rate was 68 and blood-pressure 130/80 mm. Hg. The rest of the examination was normal, apart from a systolic ejection murmur over the praecordium.

The results of investigations were as follows: radiographs of the skull, chest, and abdomen normal; Hb 13.6 g./100 ml., serum calcium 4.9 mEq/l., phosphate 4.9 mg./100 ml., sodium 133 mEq/l., potassium 4.4 mEq/l., urea 42 mg./100 ml.; S.G.P.T. 30 units; serum iron 85 µg./100 ml.; glucose tolerance—a flat curve; water load—43% excreted in four hours; salt-tasting threshold was N/5 saline; urinary 17-ketosteroids 3.8 mg./24 hr.; 17-hydroxycorticoids 3.6 mg./24 hr., which after 20 I.U. corticotrophin gel b.d. rose to 8.6 mg. on the second day and 4.8 mg. on the third day.

The patient started cortisone 12.5 mg. b.d. on 22 July and fludrocortisone 0.1 mg./day. By 25 August all symptoms had disappeared,