The mineralocorticoid effects of high dose hydrocortisone

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High dose hydrocortisone may cause life threatening hypokalaemia in predisposed subjects because of its mineralocorticoid effects

Intravenous hydrocortisone in high doses is often prescribed when immunosuppression is required urgently, such as in the treatment of acute asthma. It is also sometimes used when patients are unable to take oral prednisolone. This practice is potentially dangerous, however, as high dose hydrocortisone may precipitate clinically significant hypokalaemia in susceptible patients. The importance of this effect is emphasised by the following report.

Case report

A 63 year old man with a history of alcohol abuse presented with a two day history of haematemesis, melaena, and blackouts. He admitted drinking 3-4 litres of beer a day but denied drinking in the week before admission because of indigestion. On examination he was pale with a generalised purpuric rash. The liver was enlarged to 5 cm below the costal margin, and he had a small retinal haemorrhage. A full blood count showed a haemoglobin concentration of 51 g/l, a white cell count of $8.8 \times 10^9/l$, and a platelet count of $4 \times 10^9/l$. Electrolyte analysis showed the following plasma concentrations: sodium 131 mmol/l (normal 133-144 mmol/l), potassium 3.7 mmol/l (normal 3.4-5.2 mmol/l), total calcium 1.92 mmol/l (normal 2.26-2.60 mmol/l), urea 9 mmol/l (normal 2.5-7.5 mmol/l), and creatinine 91 $\mu\text{mol/l}$ (normal 50-100 $\mu\text{mol/l}$). A coagulation screen gave a thrombin time of 12.5 s (control 13.0 s), a prothrombin time of 14.2 s (control 13.7 s), a kaolin cephalin clotting time of 39.3 s (control 40.8 s), and a reduced thrombotest result of 60%. (The thrombotest is a combined assay of the activities of factors II, VII, IX, and X.) Liver function tests showed the following serum bilirubin concentrations: 11 $\mu\text{mol/l}$ (normal 1-17 $\mu\text{mol/l}$), albumin 24 g/l (normal 35-50 g/l), and γ -glutamyltransferase 60 IU/l (normal <45 IU/l).

An electrocardiogram showed a short PR interval of 0.08 s (figure 1). Heart size appeared normal on chest radiography, but there was some interstitial shadowing thought to be due to pulmonary haemorrhage. Ten units of platelets were given and a blood transfusion was started. A bone marrow sample and trephine biopsy specimen showed no megaloblastic features but abundant immature megakaryocytes consistent with peripheral consumption of platelets. Endoscopy showed haemorrhagic gastritis.

On the day of admission (day 0) omeprazole was started and intravenous human normal immunoglobulin (Sandoglobulin) 0.8 g/kg was given for a presumptive diagnosis of immune thrombocytopenia. Steroids were initially avoided because of the haemorrhagic gastritis, but after four days without improvement in the platelet count intravenous hydrocortisone (100 mg four times daily) was started as well as a further course of human normal immunoglobulin (0.4 g/kg/day for five days). On day 5, one day after starting hydrocortisone, serum electrolyte analysis showed hypokalaemia (potassium concentration 2.6 mmol/l, sodium concentration 139 mmol/l). Oral supplementation with potassium chloride 32 mmol (Sando-K) was tried, but it was poorly tolerated and therefore abandoned. Instead, a fluid regimen consisting of alternating 12 hour infusions of 0.9%

saline and 5% dextrose (1 litre bags) was started. The infusion fluids were each supplemented by 40 mmol of potassium chloride for the first day; potassium supplementation was then reduced to 40 mmol daily. On day 8, three days after starting this potassium regimen, serum sodium concentration was 142 mmol/l and the serum potassium concentration had risen to 2.9 mmol/l. The platelet count had risen to $110 \times 10^9/l$ and the hydrocortisone was therefore reduced to 100 mg three times daily. Intravenous infusions were then stopped as the patient had started to eat and drink.

On the morning of day 11 the patient was well and oral prednisolone 25 mg twice daily was substituted for the hydrocortisone. In the afternoon the patient's condition suddenly deteriorated and he was found unconscious with Cheyne-Stokes respiration. His pupils were fixed and dilated and he did not respond to deep pain. The doll's eye reflex was absent and his pupils were unresponsive to light. Funduscopy showed the previously noted haemorrhage and no papilloedema. During examination the patient progressively adopted a decerebrate posture with marked extensor rigidity and bilateral extensor plantar responses. His pulse was 90 beats per minute and regular and his blood pressure was 150/90 mm Hg. A full blood count gave a haemoglobin concentration of 100 g/l, white cell count of $14.5 \times 10^9/l$, and a platelet count of $212 \times 10^9/l$. An electrocardiogram showed ST segment depression and U waves (figure 2).

Basilar artery occlusion was diagnosed and computed tomography was performed urgently before the electrolyte results were available. The patient developed ventricular fibrillation in the radiology department; this was treated by DC shock. The tomogram was normal apart from showing mild cerebral atrophy. On return to the ward his neurological signs began to improve, and the electrolyte results showed marked hypokalaemia (potassium concentration 2.0 mmol/l) and hypomagnesaemia (magnesium concentration 0.5 mmol/l (normal 0.7-1.2 mmol/l)). Plasma sodium concentration was 143 mmol/l, urea concentration 3.4 mmol/l, and creatinine concentration 65 $\mu\text{mol/l}$. Serum calcium concentration was 2.17 mmol/l with an albumin concentration of 27 g/l. Concentrations of cardiac enzymes were not raised. In the first hour the patient was given 40 mmol potassium chloride and 3 g magnesium sulphate by intravenous infusion. He received an additional 4 g magnesium sulphate over 24 hours and intravenous potassium chloride at a rate of 40 mmol/h, decreasing to 20 mmol/h after two hours. Correction of the hypokalaemia took 16 hours, by which time 280 mmol of potassium chloride had been infused; plasma potassium concentration was then 3.6 mmol/l. During this period there were several episodes of torsades de pointes ventricular tachycardia (figure 3), but despite this he progressively recovered with a complete return of neurological function. Subsequent electrocardiography showed correction of the T waves and disappearance of the U waves (figure 4).

Discussion

Hypomagnesaemia is a recognised complication of chronic alcohol consumption and may be due to

Serum potassium 3.7 mmol/l

FIG 1—Electrocardiogram on admission showing short PR interval of 0.08 s

Serum potassium 2.0 mmol/l

FIG 2—Electrocardiogram after cerebral ischaemic episode showing ST segment depression and U waves

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Serum potassium 2.0 mmol/l

FIG 3—Electrocardiogram showing torsades de pointes ventricular tachycardia

Serum potassium 4.5 mmol/l

FIG 4—Electrocardiogram after recovery showing correction of T waves and disappearance of U waves

excessive urinary loss.¹² Hypokalaemia often accompanies hypomagnesaemia owing to renal potassium wasting. In our case serum potassium concentration on admission was normal, but it fell after treatment with hydrocortisone was started. Although initial attempts at restoring the potassium concentration were adequate (80 mmol was given in 24 hours), subsequent replacement was probably suboptimal, with the patient receiving only 40 mmol/day. With this regimen the serum potassium concentration rose by 0.3 mmol/l, but it fell sharply (by 0.9 mmol/l) when supplements were stopped for two days. The mineralocorticoid effect of hydrocortisone is the only reasonable explanation for this change. The delay in restoration of the serum potassium concentration and the large quantity of potassium chloride (280 mmol) required to achieve this probably reflected the considerable tissue deficit, although we did not measure tissue potassium concentrations. A reduction in serum potassium concentration of 1 mmol represents a loss of 100–200 mmol of body potassium.³ Hypomagnesaemia also probably contributed to the difficulty in achieving a normal serum potassium concentration.⁴

Hypokalaemia and hypomagnesaemia are accepted causes of torsades de pointes ventricular tachycardia and were undoubtedly the precipitants in our case. The reversible decerebrate features were probably the result of prolonged hypotension and cerebral ischaemia after an unrecognised arrhythmia. The electrocardiogram showed features of hypokalaemia as well as a short PR interval. The significance of a short PR interval was uncertain in our case as the patient had no history of palpitation or supraventricular tachycardia. Flattening of the T waves and the presence of U waves may mimic a long QT interval as the U waves may be mistaken for delayed T waves.⁵ Hypomagnesaemia is, however, a recognised cause of a prolonged QT interval.

The mineralocorticoid activity of hydrocortisone and prednisolone are almost equivalent for the same dosage (relative potency 1.0 v 0.8 respectively). Hydrocortisone, however, has reduced anti-inflammatory and immunosuppressive potency, the dose required to induce remission in immune thrombocytopenia being four times the standard dose of prednisolone (table).⁶ Consequently, at an appropriate dose for immune thrombocytopenia the mineralocorti-

coid activity of hydrocortisone is five times that of prednisolone. This may precipitate significant hypokalaemia in the presence of a low total body potassium and magnesium concentration as may apply in those taking long term diuretics and in alcoholic subjects. Dexamethasone has no mineralocorticoid activity, despite having potent anti-inflammatory activity, and has been used in immune thrombocytopenia.⁷ Methylprednisolone has less mineralocorticoid activity than prednisolone and slightly greater anti-inflammatory and immunosuppressive potency. These agents are safer for immunosuppression as they are less likely to precipitate hypokalaemia with its potentially disastrous sequelae.

Relative potencies of corticosteroids commonly used in clinical practice*

Corticosteroid	Relative anti-inflammatory potency	Relative mineralocorticoid potency
Hydrocortisone	1	1
Prednisolone	4	0.8
Methylprednisolone	5	0.5
Dexamethasone	25	0
Fludrocortisone	10	12

*Adapted from Haynes.⁶

If patients are prescribed hydrocortisone in high doses their electrolyte concentrations should be monitored frequently and any hypokalaemia should be treated promptly and adequately. Patients taking diuretics may be at greater risk. Hypomagnesaemia is frequently found in alcoholism. In these patients fluid regimens should be supplemented with magnesium as unsupplemented regimens are likely to lower serum concentrations further. Furthermore, unrecognised cardiac arrhythmias should be considered in the differential diagnosis of apparent stroke, especially when there are no localising signs. This may identify patients at risk of further arrhythmias and prevent permanent brain injury.

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A MEMORABLE PATIENT

The burnt arm

I was a senior house officer in paediatrics and had just returned to the ward from the clinic. A young mother and her daughter of a few months were on the ward. She looked tense and anxious and her daughter was fretful and crying. They were awaiting a sweat test. I set up the test and connected the electrodes to the baby's skin. A few minutes later a nurse came to me and said the mother was concerned that her baby was distressed. I went to see her, she seemed fretful as before, but on examination I could find nothing more specific and reassured the mother.

The test was duly completed, but when the electrodes were removed the baby's skin was superficially burnt. I apologised to the mother who was understandably annoyed. She explained to me that she knew her child as

she had looked after her from birth. Why hadn't I listened to her when she said something was not right?

I learnt two important lessons from this event. Firstly, if a mother tells me that something is wrong with her child I take it seriously even if I cannot find anything wrong. Secondly, I make sure I am properly familiar with equipment before I use it.

I saw this mother and her daughter a few weeks later. Her sweat test had proved positive. She was much more at ease now as she finally had a diagnosis for her baby daughter. We chatted and she showed me her daughter's arm. Much to my relief it had healed completely.—A C IRLAM is a general practitioner in Southend-on-Sea