Case reports

haemophilic child has previously been described (McCarthy and Coble, 1973).

The present case emphasizes that, with maintenance of adequate factor VIII levels, surgical intervention for cerebral haemorrhage can be undertaken without haemostatic problems. Although the ultimate prognosis was not affected here, neurosurgery should now be contemplated for this complication.

The use of the EMI scan is also illustrated here. This permits anatomical localization without invasive procedure and is of particular value in this situation.

Acknowledgments

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The use of dilute hydrochloric acid and cimetidine to reverse severe metabolic alkalosis

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Summary

Two cases of severe metabolic alkalosis associated with gastric hypersecretion were successfully treated with dilute hydrochloric acid and a histamine H2-receptor antagonist given by intravenous infusion. This combined therapy with electrolyte replacement and suppression of gastric secretion is valuable in the control of this serious metabolic abnormality when conventional treatment is unsuccessful or contraindicated.

Introduction

Patients with gastric hypersecretion associated with Zollinger–Ellison syndrome may develop severe metabolic alkalosis due to large losses of hydrogen ion. The conventional management of this acid/base disturbance is the infusion of large volumes of sodium and potassium chloride which suppress renal acid excretion and increase renal alkali excretion

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(Kassirer, Berkman and Lawrenz, 1965; Schwartz, van Ypersele de Strihou and Kassirer, 1968). This is a slow process which relies on good renal function and in some clinical situations is inappropriate or may be unsuccessful. This paper describes two cases of severe metabolic alkalosis in patients with gastric hypersecretion which were successfully treated with dilute hydrochloric acid and a histamine H2-receptor antagonist, cimetidine.

Case 1

A 22-year-old female was admitted for investigation of dyspepsia. She was known to have congenital heart disease, and at the age of 11 a Blalock Hanlon operation had been performed, following which she had led a relatively normal life with some restriction in physical activity. For one year she had complained of abdominal pain associated with nausea and vomiting. The pain was relieved by food and alkali. Barium meal examination had shown coarse gastric mucosal folds and multiple erosions in the second
and third parts of the duodenum, and she was treated initially with antacids and antispasmodics with poor symptomatic relief. Her vomiting increased in frequency and she had a number of small haematemeses. She rapidly became dehydrated and alkalotic with biochemical findings as follows: plasma bicarbonate 48 mmol/l; pH 7.58; base excess 23 mmol/l; urea 20 mmol/l; sodium 164 mmol/l; potassium 2.7 mmol/l. She was treated with intravenous sodium chloride and potassium chloride, but was noted to have an ileus. The volume of nasogastric aspirate was 2 l/24 hr and acid output was approximately 20 mmol/hr. She continued to produce large volumes of nasogastric aspirate for several days after which the ileus resolved. On resumption of oral feeding her electrolyte and acid/base abnormalities quickly returned to normal. Gastro-duodenoscopy was performed and showed oedema of the first part of the duodenum and some pre-pyloric ulceration.

The improvement in her condition was short-lived and she began to vomit and had melena stools. Her general condition deteriorated, with tachycardia, hypotension, slight pyrexia, shivering and mental confusion. It was felt that her symptoms were due to septicaemia and she was given gentamycin and erythromycin, with further intravenous fluids. Nasogastric aspiration was re-instituted but became blood-stained and, because of continued bleeding, laparotomy was performed. Before laparotomy her metabolic parameters were as follows: pH 7.38; sodium 137 mmol/l; chloride 116 mmol/l; bicarbonate 16 mmol/l; urea 2.7 mmol/l; potassium 5.2 mmol/l; haemoglobin 13 g/dl; white blood count 10.7 x 10⁹/l. At laparotomy there was a large benign ulcer situated on the pancreatic border of the second part of the duodenum. The stomach, gall bladder, biliary tract, liver and spleen were all normal. There was considerable oedema of the head of the pancreas, which was pinker than usual but the general consistency of the gland was smooth with no nodular masses palpable or visible. Truncal vagotomy and gastro-enterostomy were performed, this being the procedure most compatible with her poor clinical condition.

Postoperatively she was electively ventilated for 24 hr during which time she produced over 4000 ml of gastric aspirate. She became alkalotic and, on the first postoperative morning, her pH was 7.57 and base excess 12 mmol/l (Fig. 1 – day 0). She was treated with large volumes of sodium and potassium chloride and there was improvement over the next three days. On the fourth postoperative day she complained of weakness of the left arm and leg, and had a grand mal convulsion. On examination her general condition was poor, her pulse was 130/min and there was tachypnoea. She was pale, cyanosed and hypotensive and, although conscious, was confused and agitated. Shortly afterwards she had a left-sided convulsion during which she became deeply cyanosed and unconscious. It was thought that she might have become septicaemic, or that she had had a paradoxical venous embolus, and treatment was commenced with antibiotics, steroids and ventilation of the lungs. Biochemical findings at this time were pH 7.47; Pco₂ 34 mmHg; Pco₃ 42 mmHg and base excess 6 mmol/l (Fig. 1 – day 3). Her general condition quickly improved with intensive support but she continued to have convulsions and these were treated with thiopentone sodium. She was given sodium and potassium chloride and small amounts of glucose intravenously. She developed ileus and the volume of nasogastric aspirate increased. Twenty-four hours later her pH was 7.55, her Pco₂ 34 mmHg, her Pco₃ 42 mmHg and base excess was 22 mmol/l with a bicarbonate of 54 mmol/l (Fig. 1 – day 4). It was estimated that she had a total hydrogen ion deficit of approximately 300 mmol and it was decided that this would be best treated by direct titration with dilute hydrochloric acid via a central venous pressure line. 0.1 N-hydrochloric acid was given at a rate of 10 mmol/hr. This
produced some improvement over a 48-hr period with pH falling to 7.59; bicarbonate to 29 mmol/l; base excess of 6 mmol/l (Fig. 1 – day 6). However, the volume of gastric aspirate had increased to over 5000 ml/day and it was impossible to maintain this metabolic improvement in the face of such losses. Her general condition deteriorated and although her fits were well controlled she had marked weakness of her left side and was mentally unresponsive. A histamine H2-receptor antagonist, cimetidine, 200 mg 4-hourly intravenously, was commenced and there was an immediate reduction in the volume of the nasogastric aspirate (Fig. 2). Her metabolic abnormality was then quickly corrected with conventional therapy of sodium and potassium chloride. Her neurological signs were slow to resolve but as her neurological status returned to normal there was concurrent improvement in responsiveness. Treatment was continued with i.v. cimetidine 200 mg 4-hourly for a further 12 days, during which time there were minimal quantities of gastric aspirate, and she was then changed to the oral preparation. She made a good recovery with complete return of mental function and resolution of the left hemiparesis. Subsequent investigation has shown a high fasting plasma gastrin level (120 pmol/l) consistent with the diagnosis of Zollinger–Ellison syndrome, and at present she is being treated with oral cimetidine 400 mg 4-hourly.

**Case 2**

A 60-year-old female was admitted with a history of nausea and vomiting for seven weeks. Four days before admission her symptoms became worse with persistent vomiting, drowsiness and lethargy. She became dehydrated and for 24 hr before admission was anuric. On examination she was disoriented, markedly dehydrated and hypovolaemic. Abdominal examination revealed a tender epigastric mass and gastric succussion splash. Plain abdominal X-rays confirmed the presence of gastric distension. Initial biochemical findings were: sodium 135 mmol/l; bicarbonate 45 mmol/l; chloride 65 mmol/l; pH 7.57 (Fig. 3 – day 0). A diagnosis of severe metabolic alkalosis due to pyloric obstruction, and acute renal failure was made. Initial resuscitation was commenced with large volumes of intravenous sodium and potassium chloride and plasma. An early diuresis occurred. Nasogastric aspiration was commenced and during the first 24 hr there was a total of 2500 ml of gastric aspirate, with an acid output of 10–15 mmol/hr. The gastric aspirate was bile-stained and gastrograffin meal was performed to determine the site of obstruction. This showed widening of the duodenal loop due to obstruction by a mass in the region of the head of the pancreas, but no duodenal ulceration or pyloric stenosis. It was decided to perform a laparotomy when the metabolic alkalosis had been controlled. Conventional therapy with sodium and potassium chloride seemed inappropriate in the presence of a low urinary output (<25 ml/hr) and an elevated blood urea (228 mmol/l). Therefore an infusion of 0.1 N-hydrochloric acid in 5% glucose was given via a central venous line. The total chloride deficit was estimated to be 500 mmol and the infusion was given at a rate of 25 mmol/hr. After 18 hours' treatment, during which time 5000 ml of dilute hydrochloric acid were infused, there was no change in plasma bicarbonate and arterial pH but plasma chloride was 84 mmol/l (Fig. 3 – day 2). At this stage she developed pulmonary oedema, and the rate of infusion was reduced to 10 mmol/hr. An infusion of cimetidine was also commenced at a rate of 200 mg/4 hr, resulting in a reduction of gastric aspirate (Fig. 2). The plasma chloride and bicarbonate were normal within 48 hr and the hydrochloric acid infusion was then discounted. The cimetidine dosage, however, needed to be increased to 600 mg 4-hourly to control the volume of nasogastric aspiration. Laparotomy was performed seven
days following admission and a non-resectable tumour of the pancreas was found with evidence of secondary deposits in the liver, omentum and mesentery. Histology showed poorly differentiated adenocarcinoma. Plasma gastrin value (30 pmol/l) was at the upper limit of normal values. Her condition deteriorated and she died four days postoperatively from respiratory failure.

Discussion

Metabolic alkalosis due to the loss of large volumes of gastric aspirate is usually associated with marked reduction of extracellular and intracellular volume and total body potassium depletion. Conventional management with large volumes of sodium and potassium chloride given intravenously is a slow process and relies on good renal function for success. In certain clinical situations, when intravenous sodium chloride is contra-indicated because of acute renal failure with oliguria (Frick and Senning, 1963), cardiac failure, or where life is threatened by the metabolic abnormality, an alternative treatment should be used. Infusion of mineral acid produces effective lowering of blood pH and may be accomplished using arginine monohydrochloride, ammonium chloride or dilute hydrochloric acid (Kassirer, 1974). The amount of mineral acid required is calculated either from the extracellular chloride deficit or from the bicarbonate excess (Williams, 1976) (Table 1). Arginine hydrochloride forms hydrochloric acid during its metabolism and has been used successfully in the treatment of severe metabolic alkalosis (Randall, 1976) but its infusion may be associated with hyperglycaemia (Felig and Marliss, 1972) or may induce hyperkalaemia independent of changes in blood pH (Hertz and Richardson, 1972). Parenteral ammonium chloride carries the risk of ammonia toxicity and an appreciable concentration of ammonia enters the systemic circulation (Harken et al., 1975). Both these compounds also deliver an additional nitrogenous load and may elevate the blood urea nitrogen (Shavelle and Parke, 1975). Thus, dilute hydrochloric acid is preferable, but it should be infused via a central venous catheter to avoid local skin necrosis and tissue damage due to leakage, and the patient should be monitored closely during the infusion. Aboua, Veazey and Terry (1974) described eight cases of metabolic alkalosis due to a variety of causes which rapidly responded to infusion of hydrochloric acid after treatment with sodium, potassium, arginine and ammonium chloride had failed to correct the metabolic abnormality. This is also a valuable, safe therapy when metabolic alkalosis causes respiratory failure or severe tetany (Beach and Jones, 1971).

In cases of gastric hypersecretion, correction of metabolic alkalosis by any of the above methods is made more difficult owing to continued losses from the gastrointestinal tract. In Case 1, conventional therapy with sodium and potassium chloride corrected episodes of metabolic alkalosis pre-operatively and in the immediate postoperative period. However, deterioration in the patient's general condition on the fourth postoperative day made it essential to correct the metabolic abnormality as rapidly as possible. The infusion of 0·1 N-hydrochloric acid at
Case reports

TABLE 1. Methods of calculating amount of mineral acid required to correct metabolic (alkalosis from Williams 1976. With permission of the Editor British Medical Journal)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
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<tbody>
<tr>
<td>(i) Chloride deficit = (0.2 x body-weight in kg) x (103 - Cl- observed)</td>
<td>Calculating chloride deficit.</td>
</tr>
<tr>
<td>(ii) Hydrogen ion deficit = (0.5 x body-weight in kg) x (HCO3 observed - 24)</td>
<td>Calculating hydrogen ion deficit.</td>
</tr>
</tbody>
</table>

a rate of 10 mmol/hr produced a reduction of pH from 7.75 to 7.59, base excess from 22 to 6 mmol/l and bicarbonate from 54 to 29 mmol/l over a 48-hr period (Fig. 1). This improvement was difficult to maintain in the face of increasing gastric losses and the metabolic management was made more complex by her congenital heart disease. In Case 2, infusion of 0.1 N-hydrochloric acid at 25 mmol/hr produced no change in bicarbonate or pH but plasma chloride rose from 60 mmol/l to 84 mmol/l after 18 hr (Fig. 3). Gastric losses of chloride were not affected by the infusion, and the volume of gastric aspirate increased. Renal failure and pulmonary oedema precluded the use of large volumes of sodium and potassium chloride to correct the metabolic abnormality before surgery. In both cases improvement in general condition occurred soon after commencing an infusion of cimetidine in an effort to reduce the volume of gastric losses.

Cimetidine is a histamine H2-receptor antagonist which has been shown significantly to reduce the basal and pentagastrin-stimulated gastric secretion of patients with duodenal and pre-pyloric ulcers (Bodemar and Wallam, 1976). Preliminary results of its use in the treatment of both duodenal (Haggie, Fermont and Wylie, 1976) and gastric ulceration (Pounder et al., 1976) are encouraging. Intravenous cimetidine has been shown to reduce the volume, acid concentration and total acid output of gastric secretion during infusion in patients with duodenal ulceration (Fielding et al., 1976). It reduces gastric hypersecretion in Zollinger–Ellison syndrome (Stage et al., 1977) and is effective in the management of patients for whom surgery is unlikely to provide further benefit, or for whom it should be delayed or avoided (Misiewicz and Burland, 1976). It has also been used in the management of bleeding from the upper gastrointestinal tract due to peptic ulcer disease (Dykes et al., 1977) and liver disease (Macdougall, Bailey and Williams, 1977).

This is the first report of the use of intravenous cimetidine in the treatment of metabolic alkalosis secondary to gastric hypersecretion. In both cases, there was a rapid reduction in the volume of gastric aspirate and acid output (Fig. 2) following infusion of cimetidine at a dose of 200 mg 4-hourly, given at a rate of 100 mg/hr for 2 hr. This allowed rapid correction of the metabolic alkalosis (Figs 1 and 3). In Case 2, the dose of cimetidine had to be increased to 600 mg 4-hourly after 48 hr to maintain suppression of gastric secretion. Subsequent experience with intravenous cimetidine suggests that the above regime achieves greater control of gastric secretion than the use of bolus injections or continuous infusion.

Severe metabolic alkalosis in patients whose homeostatic mechanisms are impaired may be safely treated with dilute hydrochloric acid infusion, which should not be regarded as a therapy of desperation (Editorial, 1974). Cimetidine is an important agent in the treatment of gastric hypersecretion due to peptic ulcer disease and Zollinger–Ellison syndrome. Combined therapy with electrolyte replacement and suppression of secretion produces rapid and complete correction of severe metabolic alkalosis, and is a valuable advancement in the control of this serious metabolic abnormality in patients with gastric hypersecretion.

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References


Dermal gangrene. A rare complication of warfarin therapy

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Summary
Two cases of dermal gangrene following warfarin therapy are described and a review of the literature is given.

Introduction
Two cases of dermal gangrene have been seen following warfarin therapy. In both cases, the loading doses of warfarin were administered in the presence of impaired hepatic function and proved to be inappropriately high.

Case no. 1
A 62-year-old woman was admitted four weeks following a routine cholecystectomy with a history suggestive of multiple pulmonary emboli. Her haemoglobin was 10.2 g/dl with an iron deficiency picture, hepatic enzymes were elevated – SGOT 66 i.u./l (normal 5–17 i.u./l), SGPT 63 i.u./l (normal 5–17 i.u./l), γ GT 42 i.u./l (normal 0–16 i.u./l), bilirubin and alkaline phosphatase were within normal limits. She was given intravenous heparin 10 000 units 6-hourly for 48 hr and 30 mg warfarin orally. Two days later her prothrombin time was 44 sec (control 11 sec) so that no further warfarin was given. The next day she complained of pain in the right hypochondrium. On examination, a striking raised erythematous skin lesion measuring 8 by 4 cm with sharply demarcated edges was found to be extremely tender. A provisional diagnosis of intracutaneous haemorrhage due to overdosage with anticoagulant was made. The prothrombin time was 64 sec (control 13 sec) and 10 mg of vitamin K₁ were given intravenously. Over the next week the affected area blistered and then became necrotic; finally, being covered by a black eschar (Fig. 1). Her haemoglobin fell to 8.5 g/dl and it was eight days before the prothrombin time fell to within the therapeutic range. At this time small doses of warfarin were reintroduced without complications and the prothrombin time was satisfactory. The lesion took four months to heal, leaving only a small scar.

Case no. 2
A 49-year-old man was admitted with bacterial endocarditis on the aortic valve with severe cardiac