not important factors in these patients. Two-thirds of the children had thrombocytopenia and fulfilled all the criteria for classical haemolytic-uraemic syndrome. Some had decreased plasma fibrinogen and raised plasma haemoglobin concentrations; and the histological findings of glomerular hypercellularity and fibrin deposition with its sequelae, acute tubular necrosis and focal parenchymal necrosis, were also in keeping with a diagnosis of haemolytic-uraemic syndrome.^{6 7}

The seven patients with normal or raised platelet counts should also be considered as suffering from the haemolytic-uraemic syndrome, as such platelet values have been found in patients with this condition.^{3 5 8-10} Of the six patients whose platelet counts were not recorded, two were shown at necropsy to have renal morphology typical of the syndrome.

In every patient the renal failure was preceded by a diarrhoeal illness typical of acute bacillary dysentery. This lasted a few days and was characterised by fever, abdominal pain, and frequent passage of stools with blood and mucus. The recovery of shigellae in 30% of these patients (from an area where the prevalence of shigella infection in preschool children is 3-6.7%^{11 12}) and the finding of superficial colonic ulceration at necropsy provide additional evidence that these patients had shigellosis and not merely the non-infective bloody diarrhoea described in the haemolytic-uraemic syndrome.^{3 4}

This syndrome can be precipitated by viral infections¹³⁻¹⁶ and has followed infection with haemolytic streptococci¹⁷ or salmonellae,¹⁸ but its occurrence after shigellosis has only rarely been reported.¹⁹⁻²² We have shown for the first time that infection with *Sh dysenteriae* serotype I is an important cause of the haemolytic-uraemic syndrome.

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SIDE EFFECTS OF DRUGS

Adverse bronchial reactions to intravenous hydrocortisone in two aspirin-sensitive asthmatic patients

A leading article in the *BMJ*¹ in 1974 (based on a single case report published elsewhere²) drew attention to the possibility of allergic or idiosyncratic reactions to intravenous steroid preparations. We report two suspected adverse reactions to intravenous hydrocortisone, one of which was almost fatal. Both patients had longstanding asthma and were known to be sensitive to aspirin.

Case reports

Case 1—A 66-year-old housewife with a 32-year history of asthma had previously developed increased airflow obstruction after taking aspirin and also after a tartrazine-containing drink. She was receiving maintenance treatment with inhalational beclomethasone and salbutamol and, in addition, required prednisolone 15 mg weekly. On 16 December 1977 she was admitted electively for stabilisation after six weeks of increased wheezing. Her forced expiratory volume in one second was 0.7 l, compared with her best value of 1.5 l, and arterial blood gas estimations breathing air showed oxygen pressure 8.1 kPa (61 mm Hg) and carbon dioxide pressure 5.2 kPa (39 mm Hg). She was given nebulised salbutamol and her oral prednisolone was increased to 40 mg daily. Though she was comfortable at rest, a short course of parenteral steroids was thought to be advisable and she was given a loading dose of 200 mg hydrocortisone sodium phosphate by slow intravenous injection over two minutes. Within one minute after the injection she complained of severe breathlessness, and increased wheezing was obvious; within a further two minutes she became progressively cyanosed and suffered respiratory arrest. An endotracheal tube was inserted and she was mechanically ventilated for 11 hours. Subsequently she made a rapid recovery on increased oral steroids and is now well. The patient could recollect clearly a feeling of

rapidly progressive dyspnoea from the moment of injection of the hydrocortisone.

Case 2—This 33-year-old woman had a 12-year history of asthma and had previously developed airflow obstruction after taking aspirin. She had received large doses of oral steroids elsewhere before attending this hospital, and after the introduction of inhalational beclomethasone these were being gradually reduced. Results of a short challenge test with Synacthen (tetra-cosactrin and mannitol) suggested impaired adrenal function, and when seen in the asthma clinic on 5 August 1977 she complained of tiredness and lethargy and had a blood pressure of 105/80 mm Hg. Because of suspected subacute adrenal insufficiency (later confirmed) she was given 100 mg hydrocortisone sodium succinate intravenously. She immediately vomited and within a few minutes developed a widespread urticarial eruption and increased wheezing. She was given chlorpheniramine and increased oral steroids and made an uneventful recovery.

Discussion

Of the recognised side effects of hydrocortisone salts, anorectal pruritus is commonly associated with intravenous hydrocortisone sodium phosphate³ but the mechanism is not known. The patient in case 1 did not experience pruritus with this salt but developed severe airflow obstruction, which is unrecorded. Although there are several reports⁴ of delayed adverse reactions to intra-articular steroids (of various types), airflow obstruction has not been a prominent feature. The report of Mendelson *et al*⁵ of bronchospasm, urticaria, and angioedema occurring after intravenous methylprednisolone and hydrocortisone succinate in an asthmatic patient was the first to record an immediate anaphylactic reaction. Subsequently two more cases were reported,⁶ both in patients with airflow obstruction who were given intravenous hydrocortisone sodium succinate. The mechanism of these reactions is not known, but results of separate challenges with the active steroid preparation and the diluent⁷ suggest that preservatives or stabilisers are not responsible, and intradermal

skin tests have given conflicting results.^{2,4} Both of the reactions reported here occurred in aspirin-sensitive asthmatic patients, who react adversely to a wide range of other drugs,⁵ preservatives, and food colourings, but we are not aware of previous reactions after intravenous hydrocortisone in such patients. Possibly other cases have occurred and the increased airflow obstruction after hydrocortisone attributed to progression of asthma rather than causally related to a "safe" drug.

The present cases show the need for increased awareness of the problem, and, in aspirin-sensitive asthmatic patients at least, intravenous hydrocortisone preparations should be given only when essential and when full facilities for resuscitation are available.

We thank Dr N B Pride for advice and permission to report details of these patients, who were under his care.

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Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS

M R PARTRIDGE, MB, MRCP, registrar (present address: Department of Medicine, Middlesex Hospital, London W1)

G J GIBSON, MD, MRCP, senior registrar (present address: Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne)

Hyperosmolality complicating recovery from lithium toxicity

The increasing use of lithium carbonate in recurrent affective illnesses and the low therapeutic index of the drug demand an understanding of the management of lithium toxicity. The accepted regimen of intravenous saline¹ fails to take into account that 12% of patients taking lithium develop a diabetes insipidus-like syndrome.² Inability to concentrate urine in the presence of a continuing salt load may lead to hypernatraemia and hyperosmolality.

We describe two patients with a history of polyuria and polydipsia associated with lithium treatment who developed delirium and hyperosmolality when recovering from lithium toxicity.

Case reports

Case 1—A 63-year-old woman with a long history of recurrent unipolar depression had been treated with lithium carbonate for four years and chlorothiazide 0.5 g daily to control polydipsia and polyuria. She was admitted to hospital in April 1975 with symptoms typical of lithium toxicity, and dehydration apparently precipitated by a urinary tract infection. The plasma lithium concentration was 2.5 mmol(mEq)/l. Lithium carbonate and chlorothiazide were withdrawn, and intravenous fluid replacement with Hartmann's solution, 1 l four- to six-hourly, was begun. After initial improvement her mental state deteriorated, despite a fall in lithium concentration, improved hydration, and adequate antibiotic treatment. Tremor and neurological signs characteristic of lithium toxicity were absent during the second confusional state. Urine output was high despite raised plasma osmolality (350 mmol(mOsm)/kg) at the height of her confusion and a serum sodium concentration of 175 mmol(mEq)/l (see figure). Serum creatinine concentration ranged from 100–120 μ mol/l (1.13–1.36 mg/100 ml) from June 1974 to November 1977, reaching 190 μ mol/l (2.15 mg/100 ml) at the height of lithium intoxication.

Case 2—A 51-year-old woman had a seven-year history of depressive illnesses before being successfully treated with lithium carbonate for three years. Symptoms of polyuria and polydipsia were controlled with 0.5 g chlorothiazide daily. She was admitted to hospital with lithium toxicity and dehydration after a severe upper respiratory tract infection lasting two weeks. On admission the plasma lithium concentration was 3.4 mmol(mEq)/l and serum creatinine concentration 110 μ mol/l (1.24 mg/100 ml), later stabilising at 80 μ mol/l (0.90 mg/100 ml). Lithium carbonate and chlorothiazide were withdrawn and intravenous Hartmann's solution was given. Her clinical

state improved progressively until the fourth day after admission, when she became delirious without neurological signs of the original brain syndrome. Despite dehydration and raised plasma osmolality (325 mmol(mOsm)/kg) and sodium concentration (151 mmol(mEq)/l), urine output was high (5 l in 24 h) and the urine dilute (osmolality 165 mmol/kg) (see figure). She had no history of diabetes, but the blood glucose concentration was also considerably raised (23.7 mmol/l (427 mg/100 ml)), which contributed to the hyperosmolality. No increase in urine osmolality occurred after an intramuscular injection of 5 IU vasopressin tannate (Pitressin; Parke-Davis).

Plasma lithium and sodium concentrations, plasma osmolality, intravenous sodium intake, and start of chlorothiazide treatment (arrowed) in two patients after treatment for lithium toxicity. Normal ranges shown by broken lines.

Conversion: SI to traditional units—Plasma sodium and lithium: 1 mmol = 1 mEq. Plasma osmolality: 1 mmol = 1 mOsm.

Chlorothiazide was reinstituted after plasma lithium concentrations had dropped below the therapeutic range in both patients (see figure) to control the diabetes insipidus-like syndrome, and intravenous fluids were changed to 5% dextrose. Both patients recovered quickly. The second patient also received insulin for the temporary hyperglycaemia, which may have been related to previous consumption of high-carbohydrate fluids for thirst, though a specific effect of lithium³ cannot be excluded. No decline of renal function was observed in either patient after the acute illness and reinstatement of lithium treatment, though others have reported this.⁴

Comment

Polydipsia and polyuria are thought to be symptoms of impending lithium toxicity, but 30% of our patients have such symptoms while plasma concentrations are within the therapeutic range.⁵ Only 10% have symptoms severe enough to warrant treatment. Polyuria associated with lithium is due to failure of the kidney to respond to antidiuretic hormone (nephrogenic diabetes insipidus),¹ and is therefore partially responsive to chlorothiazide but unresponsive to vasopressin. In the presence of continuing clearance of free water intravenous replacement with isotonic saline may induce considerable hypernatraemia with consequent hyperosmolality, as seen in our patients. Although it is reasonable to attribute the initial confusional state to lithium toxicity, the deterioration in hospital occurred when lithium concentrations were falling and plasma osmolality rising. The patients began to improve when intravenous saline was withdrawn and chlorothiazide reintroduced, with consequent fall in plasma osmolality.

We concluded that, although intravenous saline may aid renal excretion of lithium, this treatment may be particularly hazardous in patients with a history suggesting lithium-induced nephrogenic diabetes insipidus. If such patients receive saline the plasma sodium concentration and plasma osmolality should be carefully monitored