this variable does not take into account the increase in workload performed at the progressive stages of the exercise test.

Headaches, the usual effect of nitrate preparations, were prominent with glyceryl trinitrate and confirmed absorption of the drug. Some patients find that when using a dental nitrate their angina is more quickly relieved after stopping exercise. This was not confirmed in our study as anginal pain passed off no sooner with the dental nitrate than with the placebo (table III). Interestingly, however, angina was promptly relieved after stopping exercise (1-68 (SEM 0-23) minutes) compared with the usual description of angina lasting five to 15 minutes.

The exact role of dental nitrates for patients with angina is uncertain. The duration of action of the two preparations assessed in this study was no longer than with oral preparations of glyceryl trinitrate 8-4 mg (Sustac) or isosorbide dinitrate 20 mg, and headaches still occurred. The preparations assessed were comparatively messy and inconvenient to use. New preparations incorporating the nitrate within a slow release plaster are claimed to have a longer duration of action and are certainly simpler to use.4 These preparations, however, are expensive and are apt to become displaced. Though sometimes recommended for nocturnal angina,5 the duration of action of up to six hours found for dental nitrates in this study suggests that they would not be active throughout sleep. There has been no study for nocturnal angina comparing a dental nitrate with an oral preparation or with a mild diuretic given in the evening.

Dermal nitrates are of undoubted value when the oral route cannot be used or when absorption may be delayed, such as before, during, or after surgery or cardiac catheterisation, in unstable angina and acute myocardial infarction, and in patients with severe heart failure. Outside these conditions no advantage has been shown for dental over oral nitrate preparations for patients with angina pectoris.

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References

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SHORT REPORTS

Persistent nephrogenic diabetes insipidus, hyperparathyroidism, and hypothyroidism after lithium treatment

Nephrogenic diabetes insipidus, hyperparathyroidism, and hypothyroidism are well recognised complications of lithium treatment that are generally considered to be reversible.1 We describe what we believe to be the first recorded case of a patient suffering all three conditions concomitantly and persistently despite withdrawal of lithium.

Case history

A 43 year old woman began treatment with lithium carbonate for mania in 1973. She continued treatment with irregular monitoring of serum lithium concentrations until her admission to Edgeware General Hospital in November 1981. At presentation she was dehydrated, drowsy, and confused with choreaathetoid movements. Results of investigations were: serum lithium concentration 2-6 mmol/l (1-8 mg/100 ml); therapeutic range 0-5-1.5 mmol/l (0-3-1.0 mmol/l); serum calcium concentration 3-0 mmol/l (12-0 mg/100 ml), and normal serum phosphate, decreased serum thyroxine, raised serum thyrotrophin, and raised serum parathyroid hormone concentrations. Correction of fluid balance and thyroid replacement led to clinical and biochemical improvement except for the serum calcium value, which remained mildly raised. She was discharged and subsequently took no more lithium.

In July 1982 she presented to another hospital for investigation of dehydration, polyuria, and polydipsia. Investigation confirmed hypercalcaemia (2-7 mmol/l (10-8 mg/100 ml)) with raised serum parathyroid hormone concentration. In addition, nephrogenic diabetes insipidus was diagnosed by a water deprivation test, during which there was a greater than 3%, loss of total body weight with failure to increase the urinary osmolality above 167 mmol (mosmol)/kg water. There was no increase in urinary osmolality after nasal administration of desmopressin. Furthermore, the plasma arginine vasopressin concentration was greatly increased at 29-7 pmol/l (32-2 pg/ml), and water rehydration decreased this. Creatinine clearance was 40 ml/min, and an intravenous urogram was normal. Serum urea and creatinine values were normal.

In October 1983 she was admitted drowsy and dehydrated. She was taking only thyroxine 125 mg daily. Serum calcium concentration was 2-8 mmol/l (11-1 mg/100 ml), serum magnesium concentration normal, and serum parathyroid hormone concentration 850 pg/ml (normal f:120 pg/ml). There was no biochemical or radiological evidence of hyperparathyroid bone disease. Correction of fluid balance produced a biochemical improvement except for the raised serum calcium value. Her clinical state was complicated by bronchopneumonia.

The combination of diabetes insipidus, hypercalcaemia, and mania presented formidable problems in maintaining fluid balance, and we therefore considered parathyroidectomy to control the hypercalcaemia. We also hoped that correction of the hypercalcaemia would improve her mental state.4 No adena was found at operation, but histological examination showed hyperplasia of all parathyroid glands. Parathyroidectomy and return of the serum calcium value to normal did not help the control of fluid balance or improve her mental state.

During March 1984 she deteriorated mentally, became dehydrated, developed bronchopneumonia, and died.

Comment

Our patient had three persistent metabolic conditions—nephrogenic diabetes insipidus, hypothyroidism, and hyperparathyroidism—after documented lithium toxicity, suggesting that lithium was responsible. These disorders are generally recognised as reversible on stopping lithium, although there are a few reports of persistent diabetes insipidus5 and hyperparathyroidism.6 Our patient continued lithium for almost eight years with irregular monitoring of serum concentrations, and it seems likely that prolonged exposure to possibly high concentrations of lithium led to irreversible changes in the thyroid and parathyroid glands and the renal tubules. Serum lithium concentrations within the therapeutic range may, however, be associated with the development of toxicity.7 Hypercalcaemia was an unlikely cause for the diabetes insipidus because the disorder persisted postoperatively when she was normocalcemic.8 This case re-emphasises the importance of regular monitoring of

BRITISH MEDICAL JOURNAL VOLUME 290 16 FEBRUARY 1985
Severe leucopenia in fatal lithium poisoning

Lithium carbonate is commonly used to treat manic depressive psychoses.1 Numerous adverse effects (some related to dose) have been described, and it is important that plasma lithium concentrations are monitored regularly so that they may be maintained within the therapeutic range of 0·6–1·2 mmol/l (0·42–0·83 mg/ml).2 Gastrointestinal, endocrine, neurological, and renal side effects are well recognised,1 and haematological abnormalities have been less commonly described.3,4 Severe toxicity may occur with plasma lithium concentrations over 2·0–2·5 mmol/l (1·4–1·7 mg/ml) and is potentially lethal.1 Therapeutic efforts to reduce plasma lithium concentrations may be hampered by continued absorption from sustained release preparations.1

We describe a fatal case of self-poisoning with lithium carbonate that resulted in severe leucopenia before death.

Case report

A 49 year old man with a long history of depression was admitted as an emergency in a stuporous and agitated state (day 1). His general health had been good, and his only regular medication was lithium carbonate (sustained release) 800 mg a day, although on occasions he had received chlorpromazine, thioridazine, fluphenazine, and benzodiazepines without ill effect. He had been found unconscious and was estimated to have ingested more than 30 lithium carbonate 400 mg tablets. He had also taken an undetermined number of tablets of chlorpromazine 25 mg, flurazepam 1 mg, and temazepam 10 mg, but there had been no more than three tablets in each container before overdosage.

On examination he was polyuric, haemodynamically stable, and breathing spontaneously. Serum lithium concentration was 3·32 mmol/l (2·3 mg/ml) (no other drugs detectable), haemoglobin concentration 14·1 g/dl, red cell count 4·99·10^12/l, white cell count 10·0·10^9/l, and platelets 283·10^9/l. Gastric lavage was performed, intravenous fluids started, and 50 ml lactulose given orally. No other drugs were administered. Five hours later the serum lithium concentration reached 5·54 mmol/l (3·8 mg/ml) (haemoglobin concentration 17·5 g/dl, red cell count 5·58·10^12/l, white cells 11·2·10^9/l, platelets 111·10^9/l) and peritoneal dialysis was started. On the morning of day 2 the serum lithium concentration reached 9·8 mmol/l (4·0 mg/ml) and while the white cell count had fallen to 1·4·10^9/l with an unremarkable differential count (74%, neutrophils, 22%, lymphocytes, 2%, eosinophils, 2%, monocytes, no basophils). The red cell count was 4·33·10^12/l, haemoglobin concentration 12·9 g/dl, and platelets 242·10^9/l.

He subsequently became hypotensive and developed type 1 respiratory failure, although there was no suggestion of any infective process at any site and the temperature remained between 35 C and 37 C. Positive end expiratory pressure ventilation and intravenous dopamine were started. Peritoneal dialysis was continued. By day 3 serum lithium concentration had fallen to 3·9 mmol/l (2·7 mg/ml) but the white cell count was 0·2·10^9/l (haemoglobin concentration 11·5 g/dl, red cells 3·97·10^12/l, platelets 111·10^9/l). Shortly after, he had an asystolic cardiac arrest and attempts at resuscitation were unsuccessful.

Comment

The major point of interest was the development of pronounced leucopenia (without appreciable changes in circulating red cell and platelet counts) associated with an acute rise in plasma lithium concentrations, which had previously been within the therapeutic range. This does not appear to have been described previously. Conversely, circulatory failure is well recognised.1 Haematological abnormalities have been described in association with long term lithium treatment. A reversible increase in circulating leucocytes may occur, and lithium might be of value in treating neutropenia induced by chemotherapy.2 Associations with leukemic conditions and megaloblastic anaemia have also been noted.3,4 Hussain et al reported on a patient maintained on imipramine and thioridazine who developed fatal aplastic anaemia 12 weeks after starting lithium 300 mg daily; the serum lithium concentration did not exceed 0·76 mmol/l (0·53 mg/ml).5 The exact mechanism of the rapid fall in the white cell count with a normal differential described here is unclear, but it may represent a direct toxic effect of lithium at high plasma concentrations on the circulating leucocytes. Whatever the mechanism, we would recommend close monitoring of the white cell count in all cases of lithium overdose.

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Inadvertent duplicate publication

Treatment of severe poisoning with slow release theophylline

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The BMJ regrets that the case report in the above article (19 May 1984, p. 1497) was substantially the same as that published in Krankenhausart (1983;56:413–23). The authors inform us that it was also published in Attendungs- und Lungenkrankenheiten (1983;9:93–8) and reported at a symposium in Vienna (Wiener Intensiv-medizinische Tage 1983). They did not, however, tell us this when the article was submitted for publication, their article did not contain any reference to the earlier papers, and all authors signed our copyright form, which states, among other things, that “papers are accepted on condition that they have not been published by any other journal.”

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