intravascular coagulation might provide a link between these two conditions.

We are grateful to Mr G Dickson for permission to report on this patient who was under his care.

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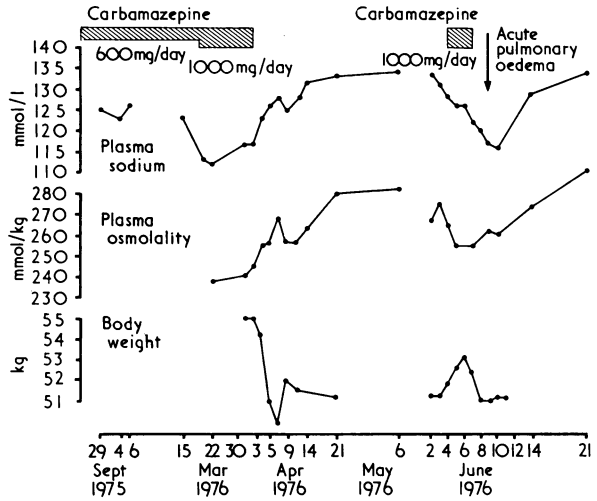
Worthing Hospital, Worthing, Sussex
I T GILMORE, MB, MRCP, medical registrar (present address: Gastrointestinal Laboratory, St Thomas's Hospital, London SE1 7EH)
E TOURVAS, MM (ŁÓDŹ) surgical registrar (present address: Harlow Wood Hospital, Mansfield)

Water intoxication due to carbamazepine

The antidiuretic effect of carbamazepine (Tegretol) is well established,[1 2] and water intoxication induced by carbamazepine has been reported in a patient with psychogenic polydipsia.[3] We have not, however, found any previous report of this complication of carbamazepine treatment in patients with trigeminal neuralgia or epilepsy. We describe here two patients, one with trigeminal neuralgia, the other with epilepsy, who developed carbamazepine-induced abnormal water retention.

Case 1

A 74-year-old man developed left-sided trigeminal neuralgia confined to the mandibular branch in 1965. He also had ischaemic heart disease and hypertension, which were treated with debrisoquine, digoxin, and amiloride with hydrochlorothiazide (Moduretic). He had had several attacks of left ventricular failure, and in 1975, when admitted with urinary retention, he had episodic confusion. His plasma sodium concentration was 123 mmol (mEq)/l, although its significance was not appreciated. His trigeminal neuralgia was well controlled by carbamazepine 600 mg/day, which he had been taking for 10 years.



Case 1. Body weight, plasma sodium and osmolality, and dose of carbamazepine.
Conversion: SI to traditional units—Sodium: 1 mmol/l=1 mEq/l. Osmolality: 1 mmol/kg=1 mOsm/kg.

In February 1976 he was admitted to Nottingham General Hospital with an exacerbation of trigeminal neuralgia and a week's history of anorexia, nausea, vomiting, and ankle oedema. Because of continuing severe pain carbamazepine was increased to 1000 mg/day. After this he became drowsy and confused. Investigations showed: plasma sodium 112 mmol/l, plasma urea 8·3 mmol/l (50 mg/100 ml), plasma osmolality 238 mmol (238 mOsm)/kg, urine osmolality 225 mmol (225 mOsm)/kg, and serum carbamazepine 31·7 μmol l (7·5 μg/ml). A chest radiograph showed no evidence of bronchial carcinoma, and water intoxication due to carbamazepine was suspected. Inferior dental nerve block with alcohol was performed. This resulted in complete relief of pain, and the carbamazepine was discontinued. After this he had a diuresis and lost 5 kg in weight, his ankle oedema cleared, and the electrolyte concentrations returned to normal within two weeks. His general condition improved remarkably and he regained his former alertness and mobility.

Although there was no doubt that he had been suffering from water intoxication, we were unsure whether carbamazepine had been responsible. Since it was possible that he might need the drug again, rechallenge was thought to be justified. Six weeks later, with his informed consent and under carefully controlled conditions in hospital, he was restarted on carbamazepine 1000 mg/day. Within three days he developed nausea, vomiting, and dizziness. By the fourth day the plasma sodium concentration had dropped to 120 mmol/l and he had gained 2 kg in weight. Serum carbamazepine was 25·4 μmol/l (6 μg/ml). The drug was stopped but eight hours later he developed acute pulmonary oedema, which was successfully treated. Within two weeks his electrolyte concentrations had returned to normal and he had regained his former wellbeing. The dose of carbamazepine, the changes in body weight, and the plasma sodium and osmolality levels are shown in the figure.

Case 2

A 38-year-old woman with a 16-year history of post-traumatic epilepsy was admitted to the Maudsley Hospital in February 1976 because of recurrent fits on multiple drug therapy. She had been taking carbamazepine 600 mg/day for 18 months and her serum level was 19·0 μmol/l (4·5 μg/ml). She was also taking phenytoin 400 mg/day, phenobarbitone 120 mg/day, diazepam 45 mg/day, and clonazepam 9 mg/day. Serum phenytoin and phenobarbitone levels on admission were within the optimum range, but she was drowsy and had gross gum hypertrophy. Serum and red cell folate levels were low, as was the plasma calcium level (2·2 mmol/l (8·56 mg/100 ml)), but the alkaline phosphatase was normal. Plasma sodium was 140 mmol/l and chloride 105 mmol (mEq)/l.

Treatment with phenytoin and phenobarbitone was withdrawn gradually and diazepam reduced to 10 mg/day. Concurrently carbamazepine was increased gradually to 1200 mg/day. Later sodium valproate 1200 mg/day, calcium gluconate 1200 mg/day, and vitamin D (calciferol) 1·25 mg twice weekly were added. During March and April 1976 her serum carbamazepine was 63·5 μmol/l (15 μg/ml) but she had no symptoms of toxicity and the dose was not reduced until 1 May, when laboratory tests showed plasma dilution with a plasma sodium concentration of 123 mmol/l and osmolality of 258 mmol/kg. Electrolyte concentrations became normal when the serum carbamazepine level had fallen to 42·3 μmol/l (10 μg/ml) and were maintained when the drug was finally withdrawn. During the period of low plasma osmolality the urine osmolality was consistently higher with values between 324 and 440 mmol/kg. Seizures remained difficult to control throughout the period of observation.

Comment

In our first case the rapid development of the symptoms and biochemical changes of water intoxication shortly after restarting carbamazepine confirmed that the drug was responsible, even though the serum carbamazepine remained within the optimum range (16·9-42·3 μmol/l (4-10 μg/ml)). This patient may have been particularly vulnerable because of his previous cardiac failure and the interaction between the carbamazepine and other drugs (debrisoquine, digoxin, and Moduretic). Our second patient was much younger and the abnormal water retention was associated with toxic levels of carbamazepine. Her electrolyte concentrations returned to normal when the dose was reduced and serum carbamazepine fell within the optimum range.

Although carbamazepine[1] has antidiuretic effects and is effective in treating diabetes insipidus,[2] its mode of action remains unclear. There is conflicting evidence from studies in which plasma antidiuretic hormone levels have been assayed, and there are few data on the effect of carbamazepine in normal people.[4 5] In our first case, although the urine osmolality was lower than that of the plasma, the difference was too small to prevent severe overhydration. In our second case the inappropriately high urine osmolality supports the hypothesis that there was an antidiuretic effect when the serum carbamazepine levels were in the toxic range.

Water intoxication as a side effect of carbamazepine may occur more often than has been recognised. Some of the common side effects of

carbamazepine are very similar to the clinical features of water intoxication. Dizziness, headaches, nausea, and mental confusion may occur with both, although it is not known what proportion of patients who develop these side effects on carbamazepine do so because of a fall in the plasma osmolality. When untoward symptoms develop during treatment and subside after the dose is reduced the mechanism of production of the side effect is usually not investigated.

Water retention may itself have an adverse effect on epilepsy,[6] and, as a result of our experience, we wonder whether this may account for the apparent failure of carbamazepine to improve the control of epilepsy in some patients. Measurement of serum drug levels now has a recognised place in the management of epilepsy, and if the serum carbamazepine level is high, as in our second case, the plasma sodium should be measured. If the sodium concentration is low the dose of carbamazepine should be reduced or stopped. Special care should be exercised when carbamazepine is given to elderly patients and those with cardiovascular disease. If symptoms consistent with water intoxication occur the plasma sodium and osmolality should be checked. Hyponatraemia is, then, another indication to reduce or stop carbamazepine.

We are grateful to Dr Geoffrey Walker, chemical pathologist, Nottingham General Hospital, for helpful advice.

ADDENDUM—Since this paper was submitted the potential dangers of carbamazepine have been emphasised by the finding of Henry *et al*[7] that symptomless hyponatraemia occurred in five out of 16 patients on carbamazepine. Although most of their patients were taking the drug for epilepsy, the cardiovascular consequences are likely to be more severe in elderly patients taking carbamazepine for trigeminal neuralgia.

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General Hospital, Nottingham NG1 6HA
W P STEPHENS, MB, senior house officer in neurology
M L E ESPIR, MB, FRCP, consultant neurologist
R B TATTERSALL, MD, MRCP, consultant physician

Bethlem Royal and Maudsley Hospitals, London JE5
N P QUINN, MB, senior house officer in neurology
S R F GLADWELL, MB, registrar in psychiatry
A W GALBRAITH, MB, clinical assistant in neurology
E H REYNOLDS, MD, FRCP, consultant neurologist

SHORT REPORTS

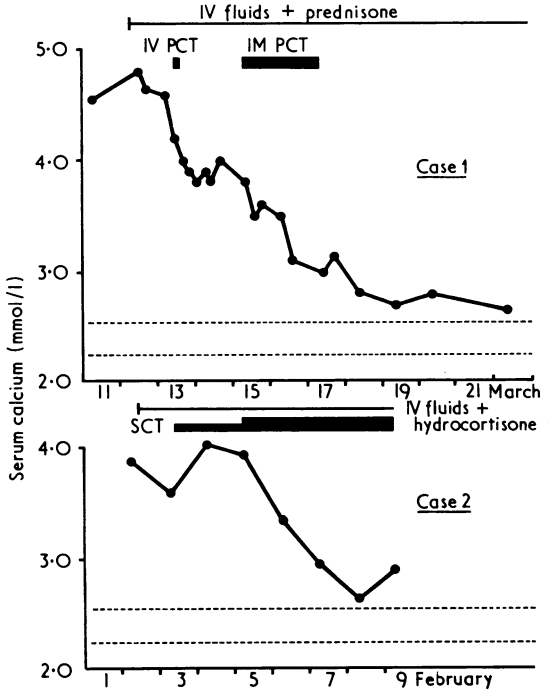
Emergency treatment with calcitonin of hypercalcaemia associated with multiple myeloma

Hypercalcaemia is a frequent complication of multiple myeloma. In an analysis of prognostic features[1] hypercalcaemia had no adverse effect on prognosis provided that the reduction in calcium concentrations was prompt and associated uraemia reversed. Such hypercalcaemia usually responds to treatment with steroids and cytotoxic drugs. Nevertheless, more severe hypercalcaemia may be immediately life-threatening and require emergency treatment. There have been reports on single cases of hypercalcaemia in multiple myeloma treated with calcitonin.[2 3] We describe two patients in whom additional treatment with calcitonin appeared to produce a useful hypocalcaemic response.

Case reports

Case 1—A 50-year-old woman presented in March 1970 with a one-month history of chest pain. Multiple myeloma was diagnosed on the basis of Bence Jones proteinuria, radiographic skeletal survey showing multiple osteolytic lesions, and an excess of plasma cells in the bone marrow. She became drowsy and nauseated. The serum calcium concentration was 4·55 mmol/l (18·2 mg/100 ml) and blood urea was 13·6 mmol/l (81 mg/100 ml). Initial treatment of the hypercalcaemia with intravenous saline, intravenous sodium phosphate, and prednisone (60 mg daily) was ineffective. After an initial intravenous infusion of porcine calcitonin (140 MRC units for one hour followed by 280 MRC units hourly for three hours) the serum calcium concentration fell to 3·8 mmol/l (15·2 mg/100 ml) and her clinical condition improved. She was started on melphalan, 8 mg daily, but no further fall in serum calcium concentration was seen until intramuscular calcitonin (640 MRC units six-hourly) was started 36 hours later. The serum calcium concentration then fell to 3 mmol/l (12 mg/100 ml). Blood urea and serum calcium concentrations were normal three weeks later.

Case 2—A 64-year-old woman presented with back pain in 1974. Diagnosis of multiple myeloma was made on the basis of free kappa light chains in serum and urine, excess of plasma cells in the bone marrow, and radiographic skeletal survey showing multiple osteolytic lesions. The serum calcium concentration was 3·15 mmol/l (12·6 mg/100 ml) but fell to normal within 12 days on treatment with melphalan and prednisone. In 1976 she developed symptomatic hypercalcaemia—with a serum calcium concentration of 3·89 mmol/l (15·6 mg/100 ml)—and had a blood urea concentration of 16·3 mmol/l (106 mg/100 ml). Salmon calcitonin, 200 MRC units subcutaneously eight-hourly, had no effect on serum calcium concentration and the dose was increased to 400 MRC units eight-hourly. The serum calcium concentration fell to 2·62 mmol/l (10·48 mg/100 ml) over the next six days.



Changes in serum calcium during treatment of hypercalcaemia. Porcine calcitonin=PCT. Salmon calcitonin=SCT. Intravenous=IV. Intramuscular=IM. Horizontal dotted lines represent upper and lower limits of normal.

Conversion: SI to traditional units—Calcium: 1 mmol/l=4 mg/100 ml.