extremities. During the intervals the patient was in a deep comatose state. The EEG showed, besides a diffuse slowing of the background activity, bursts of generalised 11–13 Hz recruiting rhythms of short duration, followed by generalised spike- and polyspike-wave discharges ending with short phases of bioelectric depression (fig). A CT scan and a lumbar puncture gave normal results. Intravenous phenytoin (750 mg/day) and phenobarbitone (200 mg/day) were started. The patient gradually improved, even though less frequent seizures were still observed over the next 24 hours. On the third day he was fully alert and was transferred to our Centre for Epilepsy. EEG abnormalities (short generalised discharges of irregular spike-wave complexes and a moderate diffuse slowing of background activity) gradually improved. When the patient was discharged, on the 30th day, he was taking phenytoin (300 mg/day) and mephobarbital (120 mg/day) and, over the next three years, he has been in good health.

The patient and his relatives gave no personal or family history of epilepsy or seizures or of alcohol abuse. However, they revealed that the patient, who was a medical student, for many years suffered from anxious neurosis and depression, partly due to his failure in school. For this reason he used to take very high dosages of benzodiazepines. During the 7 months which preceded the convulsive status epilepticus he habitually took 40–50 tablets of 5 mg diazepam (200–250 mg) every day. Since symptoms of anxiety did not cease and drowsiness and disturbances of the gait had appeared, the patient was examined by a psychiatrist who prescribed an antidepressant (maprotiline chlorhydrate, 50 mg) and recommended discontinuing diazepam, which the patient did abruptly. During the following 4 days he was especially agitated and anxious, managed to sleep only a few hours a night, experiencing terrifying dreams which, particularly during the last two days, he could not distinguish well from reality. Occasionally he had myoclonic jerks of the upper extremities, was confused and felt persecuted. On the fourth day after diazepam withdrawal, in the morning, about an hour after awakening, he had his first generalised tonic-clonic seizure.

It is known that treatment with benzodiazepines over prolonged periods can lead to physical dependence and a characteristic withdrawal syndrome.^{2–4} Seizures,^{5–8} confusional or paranoid psychoses⁹ and coma^{10,11} are the most severe withdrawal symptoms reported and are more frequently observed 2–10 days after abrupt discon-

tinuation of high dosages and/or long term treatment.⁴

In our patient the most commonly observed diazepam withdrawal symptoms (insomnia, increasing anxiety and restlessness) preceded a confusional state and then the convulsive status epilepticus. The temporal relationship and the clinical picture firmly support the hypothesis that the patient's symptomatology had been caused by the abrupt diazepam withdrawal. In fact, the administration of 10 mg of diazepam IV, when our patient was confused, produced an almost complete, although transient, disappearance of his symptoms. However, repeated administration of the drug was subsequently unable to control seizures and to prevent the occurrence of status epilepticus. We have not a clear explanation for this phenomenon although tolerance may be involved. The administration of maprotiline after diazepam withdrawal might have been a factor in causing the acute disorder of our patient. Antidepressants can lower the threshold for seizures and in some cases were considered to be a contributing factor of benzodiazepine-withdrawal symptoms.^{11,12}

G ZACCARA
P INNOCENTI*
M BARTELLI
R CASINI*
F TOZZI*
L ROSSI
R ZAPPOLI

The Centre for Epilepsy,
2nd Neurological Institute,
University of Florence, and
Intensive Care Unit,*
USL 10/D Florence,
Italy

Address for reprint requests: Dr Gaetano Zaccara, Department of Neurology, Viale Morgagni 85, 50124 Florence, Italy.

References

- 1 Marks J. *The Benzodiazepines: Use, Overuse, Misuse, Abuse*. Lancaster: MTP Press, 1978.
- 2 Petursson H, Lader MH. Withdrawal from long-term benzodiazepine treatment. *Br Med J* 1981;283:643–5.
- 3 Tyrer P, Rutherford D, Huggett T. Benzodiazepine withdrawal symptoms and propranolol. *Lancet* 1981;i:520–2.
- 4 MacKinnon G. Benzodiazepine withdrawal syndrome: a literature review and evaluation. *Am J Drug Alcohol Abuse* 1982;9:19–33.
- 5 Vyas I, Carney MWP. Diazepam withdrawal fits. *Br Med J* 1975;2:44.

* Einarson TR. Lorazepam withdrawal seizures. *Lancet* 1980;i:151.

7 Howe JG. Lorazepam withdrawal seizures. *Br Med J* 1980;280:1163–4.

8 Levy AB. Delirium and seizures due to abrupt alprazolam withdrawal: case report. *J Clin Psychiatry* 1984;45:38–9.

9 Preskorn SH, Denner LJ. Benzodiazepines and withdrawal psychosis. Report of three cases. *JAMA* 1977;237:36–8.

10 De Bard ML. Diazepam withdrawal syndrome: a case with psychosis, seizure and coma. *Am J Psychiatry* 1979;136 (1):104–5.

11 Woimant F, Liefé P, Dorey F, Mayer JM, Haguenau M, Pepin B. Sevrage aux benzodiazépines complication par coma avec rigidité de decerebration. *Presse Med* 1983;43:2765–6.

12 Haskell D. Withdrawal of Diazepam. *JAMA* 1975;233:135.

Accepted 2 November 1985

Recurrent neuroleptic malignant syndrome and hyponatraemia

Sir: The neuroleptic malignant syndrome is an uncommon acute or subacute reaction to neuroleptic medication characterised by pyrexia, muscle rigidity, altered consciousness and elevated creatine kinase (CK) levels.¹ Its cause is unknown, additional triggers are not described and recurrence has not been reported, despite reintroduction of neuroleptic therapy on frequent occasions after single episodes. We describe a patient with recurrent neuroleptic malignant syndrome associated with hyponatraemia.

In 1958 a 20-year-old man developed paranoid schizophrenia. Over the next years he received electroconvulsive therapy (ECT), chlorpromazine and lithium, haloperidol, trifluoperazine and fluphenazine decanoate. Excessive water drinking was documented on two occasions. At the age of 43 years he was prescribed only flupenthixol decanoate 80 mg fortnightly, trifluoperazine 20 mg and orphenadrine 100 mg daily.

In February 1983, aged 44 years, he had three generalised seizures. Four hours later his axillary temperature was 38.2°C and severe generalised rigidity was noted. The serum sodium (Na⁺) was 112 mmol/l, potassium (K⁺) 1.9 mmol/l, osmolality 269 mOsm/kg, and urine osmolality 450 mOsm/kg. The white blood cell (WBC) count rose to 15.6 × 10⁹/l and aspartate transaminase (AST) to 450 IU/l. Cerebrospinal fluid (CSF) examination was normal. Intravenous potassium infusions were given and fluids restricted. Ten days later serum Na⁺ was 134 mmol/l and K⁺ 2.9 mmol/l. Previous medication was restarted.

Letters

In September 1983 he stopped eating, was seen to drink water excessively and three days later became confused, incontinent of urine and vomited twice. He developed an axillary temperature of 39.5°C and stupor. The blood pressure was 130/80 mm Hg and there was severe limb and axial rigidity. The serum Na⁺ was 119 mmol/l, K⁺ 2.9 mmol/l, osmolality 257 mOsm/kg, urine Na⁺ 4 mmol/l, osmolality 234 mOsm/kg and arginine vasopressin level 1.4 pmol/l. CSF examination was normal. Intravenous potassium was again infused and fluids restricted. The CK was 6,900 IU/l and WBC 14.8 × 10⁹/l. The following day serum Na⁺ was 126 mmol/l, K⁺ 2.3 mmol/l and urine Na⁺ 101 mmol/l. Four days later the CPK was 15,400 IU/l and after eight days Na⁺ was 138 mmol/l and K⁺ 3.9 mmol/l. At no time had the patient been hyperactive or comatose and there had been no diarrhoea, persistent vomiting or diuretic administration. Blood glucose, renal and thyroid function, synacthen test and chest radiograph were normal. Urinary porphyrins, urine and blood cultures were negative.

An excess frequency of severe hyponatraemia has been reported among schizophrenic patients admitted to hospital.² These patients present in an obtunded state with seizures, vomiting and low plasma and urine osmolalities. Excessive water drinking, anticholinergic therapy and acute psychosis have been considered as possible causes. Neuroleptic drugs are rarely implicated alone, but in such cases are thought to impair water excretion by provoking inappropriate ADH secretion, rather than promoting its effect on the renal tubule.³ In this patient there were a number of possible causes of hyponatraemia, including sodium depletion and excess water drinking. The cause of the hypokalaemia was not established, but adrenergic overactivity could have contributed.

The pathogenesis of neuroleptic malignant syndrome is unknown but it is provoked by drugs with a high incidence of extrapyramidal side-effects. The initiation or alteration of such medication often precedes the syndrome by 5–15 days, but it can occur without obvious trigger after months of treatment. In these circumstances physical exhaustion and dehydration are suggested as initiating factors and water depletion is commonly present (serum Na⁺ 150–155 mmol/l).¹ The association with triggers other than direct drug effects has not been clearly shown. The current view of the aetiology implicates the basal ganglia and hypothalamus in a drug-induced state of dopamine receptor blockade.⁴ Presumably

rigidity with heat generation is of striatal origin and hyperthermia develops as a result of hypothalamic effects. In this case the recurrence of neuroleptic malignant syndrome with hyponatraemia suggests the two disorders were linked. It is feasible that a primary disturbance of water intake or inappropriate antidiuresis is related to the hypothalamic disturbance of the neuroleptic malignant syndrome. Evidence implicating catecholamine mechanisms in the regulation of water balance is incomplete, although dopamine may interact with angiotensin in the control of water intake.⁵ It remains to be seen how this unique case might relate to the pathogenesis of neuroleptic malignant syndrome.

WRG GIBB,

JA WEDZICHA,

BI HOFFBRAND

Whittington Hospital,
London N19 5NF, UK

Address for reprint requests: Dr Gibb, National Hospitals for Nervous Diseases, Maida Vale, London W9 1TL.

References

- 1 Guze BH, Baxter LR. Neuroleptic malignant syndrome. *N Engl J Med* 1985;313:163–6.
- 2 Gleadhill IC, Smith TA, Yium JT. Hyponatraemia in patients with schizophrenia. *South Med J* 1982;75:426–8.
- 3 Miller M, Moses AM. Drug-induced states of impaired water excretion. *Kid Int* 1976;10:96–103.
- 4 Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? *Neurology* 1981;311:132–7.
- 5 Fitzsimons JT. The physiological basis of thirst. *Kid Int* 1976;10:3–11.

Accepted 5 January 1986

High plasma osmolality following intravenous dimethylsulphoxide in the treatment of post-operative hemiplegia

Sir: Dimethylsulphoxide has been used in North America to treat a wide variety of disorders.¹ In Britain it has been used topically as a vehicle for drug delivery, for bladder instillation to treat interstitial cystitis and for a number of other disorders including rheumatoid arthritis.² There is evidence that intravenous dimethylsulphoxide is useful in management of post-operative hemiplegia.³ Marked disturbances in serum osmolality

and electrolytes during intravenous dimethylsulphoxide therapy have been reported, each associated with the death of the patient.^{4,5} We report details of a case of post-operative hemiplegia treated with intravenous dimethylsulphoxide where the clinical, pharmacological and biochemical data suggest that the electrolyte disturbances are due to an osmotic diuresis caused by high plasma and urine concentrations of dimethylsulphoxide.

A 33-year-old man underwent a right frontal craniotomy for partial removal of a known craniopharyngioma with suprasellar extension. Eight hours after the operation he developed a right-sided hemiparesis, and his left pupil was fixed and dilated. Intravenous dimethylsulphoxide therapy was commenced. A 40 g loading dose over forty minutes was followed by 3 g/kg/day over a two day period, then 1.5 g/kg/day for four days when the drug was discontinued. Twenty four hours after the operation the patient was alert and conscious but the focal neurological signs remained. He had a high urine output with a low specific gravity and so desamino-arginine vasopressin 1 µg intramuscularly b.d. was commenced (pre-operative assessment had shown normal posterior pituitary function). Haemoglobin was present in the urine. From day five after operation onwards there was a progressive deterioration in consciousness level associated with pyrexia, leucocytosis and a falling haemoglobin concentration. On day seven he developed clinical and radiological signs of chest infection, and despite resuscitative measures, died on the tenth post-operative day. Necropsy revealed bronchopneumonia and pyogenic pericarditis. Dissection of the brain confirmed the presence of a partly removed craniopharyngioma involving the optic chiasma and pituitary stalk. There was an infarct transecting the internal capsule in the right caudate nucleus and ischaemic damage to the basal ganglia.

The table shows the post-operative increase in his measured plasma osmolality. Much of the increased osmolality can be accounted for by the plasma concentration of dimethylsulphoxide and its major metabolite dimethyl sulphone. There was also an increase in calculated osmolality with marked hypernatraemia and high intracellular sodium concentration compatible with water depletion totalling 6.6 litres over seven days. This deficit was in close agreement with the fluid balance charts. Urine output averaged 3130 ml per day over this period. Measured sodium intake and output were roughly equal. The plasma urea concentration increased from 5.1 to