Letters

Rapid development of hyponatraemia during low-dose carbamazepine therapy

Sir: Carbamazepine is widely used in the treatment of epilepsy and of trigeminal and other neuralgias. More recently it has found a role in the prophylaxis of affective disorders.1 It has also been given to patients with cranial diabetes insipidus,2 in whom it may stimulate arginine-vasopressin release,3 or potentiate its action on the renal tubules.4 In contrast it has only a minor effect on renal control of fluid balance in normal individuals5 and, although hyponatraemia is a well-recognised side-effect of carbamazepine therapy, it has previously been reported only at moderate or high doses and usually after weeks or months of treatment.6-11 I report the syndrome of inappropriate antidiuresis as a much earlier side-effect of carbamazepine administration at very low dosage.

A 62-year-old woman suffering from a depressive neurosis was treated with carbamazepine for cervical neuralgia secondary to chronic rheumatoid arthritis. After seven days of treatment at 100 mg twice daily increasing to 100 mg three times daily, a routine estimation of plasma electrolytes gave a sodium of 121 mmol/l with a chloride of 89 mmol/l; other results were within normal limits. Estimation of plasma and urine electrolytes confirmed the diagnosis of the syndrome of inappropriate ADH secretion according to the criteria of Bartter and Schwartz.12 Carbamazepine was discontinued, leading to a rise in plasma sodium to reach a normal value after two weeks. Physical examination and investigations, including chest and skull radiographs, showed no alternative explanation for the hyponatraemia.

The suspected role of carbamazepine in producing this effect was confirmed by a period of re-challenge with the drug, during which plasma electrolytes and carbamazepine levels were monitored daily. The dose given was 100 mg on the first day and 100 mg twice daily thereafter. On day 3, after a total dose of 300 mg, the sodium level was 135 mmol/l, just below the laboratory's normal range of 137-145 mmol/l. The following day it was 128 mmol/l with a plasma osmolality of 255 mmol/l and urine osmolality of 325 mmol/l. The corresponding carbamazepine levels were 5 and 6 mg/l (therapeutic range 3-13 mg/l); the therapeutic values at low dosage presumably reflected the relatively low body weight of the patient. On stopping carbamazepine, the electrolytes returned to normal in four days. At no time during either period of hyponatraemia did the patient show symptoms.

This case demonstrates the potentially profound disturbance of water balance which can occur as a result of carbamazepine therapy. It shows that this side-effect can occur at lower doses and after much shorter periods than has previously been recognised. It suggests the need to estimate plasma electrolytes in patients complaining of side-effects such as nausea, headache and dizziness— all symptoms of hyponatraemia—in the first few days of carbamazepine therapy.

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References

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Olfactory tubercle choline acetyltransferase activity in Alzheimer-type dementia, Down's syndrome and Huntington's disease

Sir: There have been two recent reports of neurofibrillary tangles and cell loss in the anterior olfactory nucleus in Alzheimer's disease.1,2 Our present observations of reduced choline acetyltransferase (CAT) activity in the olfactory tubercle in cases of Alzheimer-type dementia support the suggestion made in these two papers that the olfactory system may be defective in Alzheimer type dementia.

Ten cases of Alzheimer-type dementia (age range 59-90 years), three cases of Down's syndrome (aged 56, 61 and 63 years), three cases of Huntington's disease (aged 51, 64 and 68 years) and fifteen age-matched controls were studied. Five cases of Alzheimer-type dementia (1 female and 4 male) had onset of symptoms before age 65 years (pre-senile), and five Alzheimer-type dementia cases (4 female and 1 male) had onset after 65 (senile). The interval between death and necropsy was: Alzheimer-type dementia mean 16 ± 10 h SD; Down's syndrome 23, 24 and 42 h; Huntington's disease 8, 22 and 39 h; controls 16 ± 9h. Brains from the cases of Down's syndrome showed the features of Alzheimer-type dementia, that is cortical atrophy and numerous plaques and tangles in the frontal and temporal cortex. The cases of Alzheimer-type dementia and Huntington's disease showed the clinical and neuropathological characteristics of the respective diseases. The controls had no clinical signs of involvement of the central nervous system. In four out of six Alzheimer-type dementia cases, globus pallidus plaques were observed in an area which comprised the anterior perforated substance and the olfactory tubercle; plaques were much less frequent. In two Alzheimer-type dementia cases and seven
controls, no plaques or tangles were seen. CAT was measured in the olfactory tubercle, dissected to exclude the anterior perforated substance.

The activity of CAT in olfactory tubercle from the cases of Alzheimer-type dementia (mean 56 ± 40 SD nmol/h per mg protein) was considerably less (p < 0.001, Student's t test) than in the controls (153 ± 32) – see fig. Similarly low levels of CAT were observed in Down's syndrome (29 ± 22) and in Huntington's disease (34 ± 13). CAT activity in tubercles from the five female Alzheimer type dementia cases (32 ± 37 nmol/h per mg protein) was less (p < 0.05) than for the five male Alzheimer-type dementia cases (81 ± 26), but there was no significant difference between enzyme activities in five female (142 ± 17) and ten male (158 ± 38) controls. In control olfactory tubercles, CAT activity was weakly correlated (r = -0.54, p < 0.05) with post-mortem interval but not significantly related to age.

The olfactory tubercle and ventral striatum contain neurons which have very similar afferent and efferent connections. In Huntington's disease there is a loss of neurons and CAT activity from the striatum. The reduced CAT observed in the tubercle in this disease may therefore be related to degeneration of striatal-like neurons or their connections in the tubercle. In Alzheimer-type dementia and Down's syndrome, reduced CAT of the order observed in the tubercle (63% and 81%, respectively) has been found in another area of the rhinencephalon, namely the amygdala, in which plaques and tangles are very numerous. These results, combined with those of Averback and Esiri and Wilcock, suggest that olfactory regions of the brain are severely affected in Alzheimer-type dementia and in cases of Down's syndrome with the neuropathological features of Alzheimer-type dementia. We are currently investigating whether Alzheimer-type dementia patients have a deficit in their sense of smell.

For the supply of necropsy brains, we thank clinicians and pathologists of Bangour Village, Bangour General, and Gogarburn Hospitals, West Lothian; Strathmartine and Ninewells Hospitals, Dundee; and the Royal Edinburgh, Royal Infirmary and Western General Hospitals, Edinburgh. We are indebted to Mr C Farquhar for technical assistance.

Fig CAT activity in olfactory tubercle from controls and cases of Alzheimer-type dementia (ATD), Down's syndrome and Huntington's disease.

References

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High density lipoprotein cholesterol in transient global amnesia

Sir: Since the original report by Fisher and Adams, transient global amnesia has been considered to be a sudden loss of short-term memory characterised by transient inability to form new memories, repetitive queries, retrograde amnesia and absence of other neurological symptoms and signs. Although the aetiology is uncertain, most opinions favour a vascular or epileptic mechanism.

In recent years low levels of high density lipoproteins or low ratio of high density lipoprotein cholesterol to total cholesterol have been related to an increased risk of myocardial infarction and cerebrovascular disease. Recent studies have shown that high density lipoprotein cholesterol to total cholesterol ratios are related to severity of coronary artery disease more than high density lipoprotein cholesterol level above. Sirtori et al reported a decreased high density lipoprotein cholesterol level in men with transient ischaemic attacks, but there are no previous reports of this determination in transient global amnesia.
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