LETTERS TO THE EDITOR

Mechanisms of carbamazepine-induced antidiuresis

Carbamazepine may cause water retention and hyponatraemia. Cecil's *Textbook of Medicine*, Harrison's *Principles of Internal Medicine*, The *Textbook of Internal Medicine* and the *Oxford Textbook of Medicine* attribute the mechanism to an excessive release of arginine vasopressin (AVP) from the neurohypophyseal system. The *Oxford Textbook of Medicine* states that carbamazepine does not augment AVP at renal tubular level. In *Brain's Diseases of the Nervous System*, the precise mechanism is noted to remain unclear. In contrast, Goodman and Gilman's *The Pharmacological Basis of Therapeutics* notes that carbamazepine has an antidiuretic effect that is sometimes associated with a reduced AVP level and indicates that the mechanisms of water retention are not clearly understood. However, the *Martindale Extra Pharmacopoeia* while citing references which support both central and renal mechanisms, clearly notes that carbamazepine sensitises the kidney to the effects of vasopressin.

The exact mode of action of carbamazepine is controversial. There is evidence that the drug may stimulate the central release of AVP either directly¹⁻³ or by altering the threshold of the hypothalamic osmoreceptors,⁴ while others claim that it increases the effect of AVP on the kidney.⁵⁻⁸ A reduction in vasopressinase activity is another possibility. These effects need not be mutually exclusive. The two case reports citing a central effect of carbamazepine found inappropriately raised AVP levels during hyponatraemia^{1,2} but both were taking other drugs.

Sorensen and Hammer³ found no change in the basal plasma AVP level with carbamazepine although the plasma osmolality had significantly decreased. This suggests a different renal response to the same AVP exposure and their conclusion that there was no direct renal effect seems unlikely. Meinders *et al*⁵ had originally reported a fall in plasma AVP with carbamazepine therapy and having found an antidiuretic effect of the drug on patients with cranial diabetes insipidus, they concluded that the mode of action was renal and not central. While examining the relationships between plasma and urine sodium, osmolality, and AVP levels in normal subjects, Thomas *et al*⁴ found that the slope of the regression line relating plasma or urine AVP to urine osmolality was not increased by carbamazepine treatment. The drug did not result in a higher urine osmolality for a given amount of AVP. They also found that both plasma AVP concentration and urine AVP excretion rate were reduced by the drug and there was a significant rise in the plasma sodium compared with a control day. Having ruled out a direct renal and a central stimulatory effect on AVP secretion, they concluded that carbamazepine reset the osmotic threshold for AVP release without affecting osmotic control around the new threshold.

Yet they acknowledged that the mechanism for the production of carbamazepine-related hyponatraemia was unclear.

While studying carbamazepine effects in normal subjects, Stephens *et al*⁶ found no direct stimulation of AVP secretion but in contrast to Thomas *et al*⁴ they found that there was an increased renal sensitivity to AVP. The AVP values found at peak diuresis when taking the drug were similar to controls despite an impaired water handling. They also suggested that there was osmoreceptor resetting so that AVP secretion was inadequate in dehydration but was in relative excess during water loading. AVP basal values were again lowered by the drug. When a patient with carbamazepine-induced hyponatraemia was treated with demeclocycline, free water clearance rose despite an increase in plasma AVP, providing further support for a direct renal action of carbamazepine.⁷ Demeclocycline has been successfully used in a similar patient following the failure of phenytoin, water restriction and carbamazepine dose reduction to correct the hyponatraemia.⁸ Further recent evidence suggests that plasma AVP may be decreased by carbamazepine even though urine osmolality increases and that plasma cortisol is increased. This may indicate that carbamazepine has an AVP-like action or that it increases the sensitivity of the AVP receptor to its agonist in both the kidney and the corticotroph in the anterior pituitary gland.⁹

The standard textbooks should be modified to encompass the diversity of the individual response to carbamazepine evident in the literature.

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Acute transient hydrocephalus in carbon monoxide poisoning: a case report

The pathological changes most commonly seen in carbon monoxide poisoning are in the region of the globus pallidus bilaterally, and less commonly in the medial temporal lobes and the cerebral white matter.¹⁻³

These pathological findings have been well correlated with CT appearances.⁴ We report a case of acute carbon monoxide poisoning with CT scan appearances of bilateral cerebellar swelling causing acute hydrocephalus. The hydrocephalus was transient and subsided on medical therapy.

A fifty six year old man was admitted unconscious after exposure to automobile exhaust fumes in a closed car. Initial examination revealed a Glasgow Coma Scale (GCS) of 6/15 (E = 1/4, V = 1/5, M = 4/6). His pupils were small and reacted sluggishly, vital signs were within normal limits, and he was breathing spontaneously. The initial blood gas analysis revealed a pH 7.07, PCO₂ 3.8 kPa, PO₂ 38.4 kPa, bicarbonate 20.3 mmol/l, and a base excess of 0.3. A toxicology screen for paracetamol and salicylates was negative. There was a neutrophilia of 27.7 × 10⁹/l. The carboxy-haemoglobin level on admission was 22%. Closed circuit high concentration oxygen (100%) was administered and one hour later a repeat carboxy-haemoglobin level was down to 5%. About eight hours later he had improved with a Glasgow Coma Scale of 13/15 (E = 3/4, V = 4/5, M = 6/6), and gave details of his suicidal attempt.

His condition deteriorated over the next twenty four hours, he became more drowsy and developed Cheyne-Stokes breathing. A CT scan showed obstructive hydrocephalus with cerebellar swelling and compression of the fourth ventricle (fig a). There was also a coexistent small left occipital low attenuation lesion. He was then transferred as an emergency to the neurosurgical service at the Royal Preston Hospital. His neurological state showed a GCS of 7/15 (E = 2/4, V = 2/5, M = 3/6), small equal sluggishly reacting pupils, restriction of external ocular movements in all directions of gaze and stable vital signs. Active surgical drainage of the hydrocephalus was considered, but it was decided to act conservatively at first. He was treated with supportive measures using dexamethasone four milligrams four times a day, O₂ inhalation and intermittent mannitol. He continued to improve over the next seventy two hours, and was then fully conscious with a GCS of 15/15. He had no focal deficits except for signs of mild cerebellar ataxia. The patient was discharged after six days when he was mobile having made a full recovery except for a mild ataxic gait. When seen at outpatients six weeks later he was asymptomatic. A repeat CT scan (fig b) showed complete resolution of the hydrocephalus and normal appearance of the posterior fossa structures. An occipital porencephaly was noted in the area of the occipital infarct. The normal blood carboxy-haemoglobin concentration is about 0.5-0.8%. It has a very high affinity for haemoglobin, about 218 times that of oxygen. The toxic effects of carbon monoxide on the tissues is due to hypoxia. The clinical picture depends on the level of carboxy-haemoglobin levels in the blood: a level less than 10% produces few symptoms; 10-30% produces headaches, mild CNS dysfunction, with decreased visual acuity and impaired cognitive functions; 30-40% produces severe headaches, dyspnoea on exertion, nausea, vomiting, impaired visual acuity, ataxia and collapse; and with levels over 40% convulsions, coma, respiratory and cardiac failure occur. Recovery is possible if exposure is terminated early and the reversal

Figure (a + b) CT scans showing hydrocephalus 24 hours after admission and resolution of hydrocephalus six weeks later.

is expedited by breathing oxygen, preferably under pressure.

The classical structural damage caused by carbon monoxide poisoning is a diffuse hypoxic cerebral injury leading to infarction. The most common lesions are of the pallidum bilaterally and are predominantly in the anterior two thirds, and probably result from the sensitivity of this functional end arterial area to hypoxaemia and hypotension. A unilateral pallidal lesion and marked asymmetrical white matter involvement has been described.⁵ The unique feature of our case is acute obstructive hydrocephalus associated with bilateral cerebellar swelling and compression of the fourth ventricle. No involvement of the globus pallidus and medial temporal lobes was seen. The precise cause of this cerebellar oedema is unknown, but could have been due to acidosis and hypoxaemia which are a common cause of widespread white matter oedema in CO₂ poisoning. The hydrocephalus was of a transient nature since it subsided on medical therapy. Bilateral cerebellar oedema in acute carbon monoxide poisoning, presenting with acute hydrocephalus, has not been previously reported. It is important to be aware of this complication in the initial stages, as a CSF diversion procedure might be required if it does not respond to steroids.

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Benign relapsing meningo-encephalomyelitis

Monteiro and Correia¹ described a 16 year old man who presented with three attacks of meningo-myelitis over a period of six years. In the third attack he also had encephalitis. We describe a young woman with frequent, relapsing and remitting meningo-encephalomyelitis.

A 19 year old woman presented with a two week history of sore throat, frontal headache and sinus infection with arthralgia and myalgia. She had acute urinary retention, pyrexia and a major seizure. In the subsequent 20 months she has had a relapsing and remitting neurological illness, the relapses typically lasting 14 days. There have been continuous inflammatory changes in her CSF. Many of the relapses have been associated with pyrexia, and she has frequently demonstrated Lhermitte's sign and Uhthoff's phenomenon. There have been numerous separate episodes of neurological signs indicating lesions involving, the cauda equina on two occasions, the brainstem and cerebellum on four occasions, the spinal cord once, and the optic nerves bilaterally twice with three separate attacks of right optic neuritis. She had complex partial seizures and four major seizures controlled by treatment with carbamazepine.

On first admission a 10 day course of ampicillin and tetracycline was prescribed without benefit. Subsequently she has been treated with maintenance low dose prednisolone and pulsed methyl prednisolone for relapses.

Normal investigations have included; a complete infectious disease screen for all bacterial, viral and fungal causes (HIV antibody testing on two separate occasions was negative); a complete immunological and connective tissue disease screen, serum angiotensin converting enzyme levels, liver biopsy, Kvem biopsy, chest radiographs, cerebral angiography and repeated CSF for

IgG, oligoclonal bands and cytology. Her HLA type is A1, A2, B8, B18, DR3 and DR4.

The main abnormality of the CSF was a variable lymphocytic pleocytosis in 11 lumbar punctures (range 6-268 cells). On three occasions the CSF protein was raised (0.60-0.70 g/l). Glucose levels have been normal.

During a 20 month period, five MRI brain scans have been performed. The first, a month after the initial presentation was normal. The second, three months later, showed an area of high signal in the right cerebellar hemisphere on T₂ images and correspondingly an area of low signal on the IR scan. At 12 months a third MRI showed several areas of increased signal on T₂ images; in the left middle cerebellar peduncle extending into the anterior aspect of the left cerebellar hemisphere, with a corresponding area on the right side, and also on the medial aspect of the right temporal lobe. These areas enhanced with intravenous gadolinium. Sixteen months after presentation a fourth MRI showed widespread T₂ increased signal changes localised in the left fronto-parietal area involving both white matter and cortex, the left optic tract, the right temporal lobe, the corpus callosum and the right brainstem, extending into the right cerebellar peduncle. The areas involved were more extensive than those seen previously. Her most recent MRI scan, three months later, showed further new gadolinium enhancing lesions in the right temporal and parietal lobes, with resolution of some of the other lesions seen on earlier scans. The new enhancing right parietal lesion (fig) was biopsied stereotactically. Histology was non-specific with an excess of astrocytes in the cortex and more prominently in the white matter with oedema, narrow perivascular cuffs of myelin pallor and small numbers of foamy macrophages.

Neurophysiological investigation showed that the previously abnormal visual evoked responses (VERs) became normal following the first episode of bilateral optic neuritis. After further attacks of right optic neuritis,

Figure Axial T₂-weighted MRI (SE_{500/15}) at 1.5T, acquired 10 minutes after intravenous gadolinium DTPA 0.1 mmol/kg. There is a large enhancing lesion involving the right parietal cortex and adjacent white matter.