# 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 directly[1-3] 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 Hammer[3] 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, $PCo_2$ 3·8 kPa, $PO_2$ 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 × $10^9$/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 occular 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, $O_2$ 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 is 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