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Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic

Sir: Carbamazepine is known to cause atrioventricular conduction block but has not yet been implicated in sudden unexpected death in epilepsy. We report one such death which, we suggest, may have resulted from ventricular arrhythmia induced by carbamazepine.

A 20-year-old student teacher presented for routine review with a 7 year history of intractable petit-mal but with well controlled grand-mal epilepsy. She was taking valproate 400 mg tds and pethadione 300 mg bd. Troxidone and ethosuximide had failed to control her petit-mal. A fresh history elicited features of temporal lobe epilepsy coinciding with her absences, namely *deja-vu, jamais-vu*, and amnesic spells. There were prodromal symptoms (strange epigastric sensations, extreme pallor) and postictal features (headache, unsteadiness). A review of her EEGs showed excess slow wave activity in the right frontal region in 1978 and in repeat EEGs in 1979, 1980 with a normal CT brain scan. The diagnosis was changed to temporal lobe epilepsy. Pethadione was withdrawn and carbamazepine was started 200 mg bd. After 3 days, her mother reported that she began to suffer syncopal episodes within a few hours of starting treatment. These were different from any previous seizures, lasted a few minutes, were preceded by lightheadedness, and were followed by total recovery. Her family doctor visited and witnessed a typical attack. She became pulseless with no heart sounds. Resuscitation was unsuccessful. Necropsy revealed normal heart, brain and lungs, except for aspiration of stomach contents. There was no evidence of an overdose, anticonvulsant levels of the previous month were within therapeutic range and microscopic examination of the heart was normal.

The annual mortality rate in patients with epilepsy has been calculated as 7.8 per 100,000 population. This is three and half times that to be expected in all age groups up to the age of 50 years. Thirteen per cent of these are sudden and unexpected and sometimes, but not always, occur after a seizure. This incidence has proved remarkably constant over a 50 year period, 

Despite advances in treatment, and affects 1:500 to 1000 epileptics. This population has been studied closely, and has been found to have a mean age of 33 years, and a seizure frequency of less than 1 a month. Their anticonvulsant levels are almost always below the therapeutic range and are often absent. They have no other medical history.

Various reasons have been advanced for this phenomenon: autonomic collapse, disruption of the cardiac and respiratory centres in the brain stem, pulmonary oedema and cardiac arrhythmias.

Autonomic disturbance is known to occur during a fit; tachycardia, a rise in blood pressure, ventricular tachycardia and both major and minor ischaemic changes on the ECG have been documented. Pulmonary oedema following a fit has been well recognised for many years and as early as 1910, this was described as a “typically present” post-mortem finding in epileptics, and as a frequent and dangerous condition following even single grand mal seizures. More recently, recurrent post-ictal pulmonary oedema has been reported in one patient, following three separate seizures, and a post-mortem study of eight young epileptics who died suddenly, revealed pulmonary oedema in all cases, with no myocardial lesion. By way of contrast, another post-mortem study of nine such patients showed myocardial changes reminiscent of the lesion of ischaemic cardiomyopathy, but no pulmonary oedema. In both studies, anticonvulsant levels were low or absent. Experimental evidence shows that lesions of the hypothalamus can produce pulmonary oedema and that this is mediated by the sympathetic output.

Furthermore, electrical stimulation of the hypothalamus can produce ventricular tachycardia and can cause ischaemic damage to myocardium similar to that caused by the injection of catecholamines.

It has, therefore, been postulated that hypothalamic injury initiates an adrenergic discharge, resulting in death by pulmonary oedema or ventricular arrhythmias. A change in permeability of the pulmonary vasculature is also thought to occur, but no mechanism has yet been proposed.

Our patient, however, had no pulmonary or cardiac lesion, although a latent electrophysiological conduction abnormality cannot be excluded. Her anticonvulsant levels were within the therapeutic range one month before her death, and she had not taken an overdose of carbamazepine, nor of any other drug. Abrupt withdrawal of paracetamol is not associated with serious adverse effects, such as autonomic epilepsy, although withdrawal of a related oxazolidine, trimethadione may precipitate fits. However, carbamazepine is known to affect the myocardium in pharmacological studies and to cause Stokes-Adams attacks and conduction block in clinical practice.

Carbamazepine is a group IA anti-arrhythmic which blocks the fast inward sodium current during the depolarisation of the cardiac membrane. It increases atrioventricular conduction time in *in vivo* and depresses ventricular automaticity in *in vitro* by reducing the rate of phase 4 depolarisation. There are nine reported cases of carbamazepine causing atrioventricular conduction block or bradycardia when taken in therapeutic doses.

Stokes-Adams attacks occurred in two patients, complete heart block in five, and bradycardia in two other patients. In all cases, sinus rhythm was re-established after withdrawal of the drug. In the five cases which were mainly monitored, the conduction block reappeared on restarting carbamazepine.

Six of the nine cases had previous ECGs available for analysis; left anterior hemiblock was present in two cases and no abnormality in three cases. There appeared to be no relation between these pre-morbid traces, the severity of the later conduction block or the dose of carbamazepine. In fact, a daily dose of only 200 mg produced Stokes-Adams attack in one patient with a previously normal ECG. Nonetheless, it has reasonably been suggested that a latent defective conduction system might be a necessary pre-requisite for the induction of atrio-ventricular block. Some support for this comes from a small pilot study on patients with pre-existing block whose ventricular standstill time, or pre-automatic pause, was significantly prolonged when carbamazepine was administered. It should also be noted that heart block may intervene after many years of carbamazepine therapy and that it may last for three or four days. It has thus been
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recommended that, in elderly patients at least, it would be prudent to perform an ECG prior to starting carbamazepine therapy.  

All nine cases described so far, have been elderly and only one patient has had epilepsy. No fatalities have been reported, and in the two detailed post-mortem studies on sudden death in epileptics, only one was taking carbamazepine, but not in the therapeutic dosage. We suggest, however, that carbamazepine was responsible both for the syncopal attacks and the death of our young epileptic probably causing ventricular asystole.

The lesion to be drawn would seem to be that any patient on carbamazepine, for whatever reason, who complains of syncope or a change in seizure type, should be admitted for investigation of this atri-ventricular conduction system.

The differentiation of cardiac and epileptic loss of consciousness can often be difficult and the temptation to increase the dose of carbamazepine in an epileptic who complains of loss of consciousness should be resisted until assessment of their cardiovascular status is complete. If in doubt, it is probably best to stop the drug and substitute an alternative. It may be prudent to perform an ECG in the elderly, before commencing treatment with carbamazepine, but, in the absence of further data on death related to the drug, no further precautions can be justified.

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Correction


Notice

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