SHORT REPORT

Amnesic syndrome after theophylline associated seizures: iatrogenic brain injury

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Abstract

Two patients developed a disabling amnesic syndrome after seizures associated with oral theophylline treatment. Such seizures are more likely in the elderly, in the presence of pre-existing neurological disease, and when theophylline is given with certain antibiotics and cimetidine. The mechanism of neuronal injury may be by the excessive release of endogenous excitotoxic glutamate.

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Although theophylline toxicity is known to induce seizures at high serum concentrations, recent reports indicate that seizures in both children and adults may be associated with therapeutic or mildly toxic concentrations.^{1,2} The prognosis for such seizures is usually benign³ but in some circumstances epileptic activity may be prolonged, focal in nature, resistant to treatment, and with a poor outcome.⁴ In one United States study of 12 elderly patients with theophylline induced seizures death occurred in eight, persistent neurological deficits in three, and good recovery in only one.² The possibility that seizures associated with chronic oral theophylline treatment may result in brain injury is not generally recognised.³ We report two patients with theophylline associated seizures who subsequently developed a persistent amnesic syndrome.

Case reports

Case 1

A 68 year old man, weight 62 kg, with a history of obstructive airways disease was admitted for anterior resection of a Dukes A carcinoma of the rectum. He had a history of alcoholism 20 years previously. Recovery after operation was complicated by prolonged ileus and a chest infection. While on an oral aminophylline (four tablets daily, each of 225 mg) three weeks after the operation he developed status epilepticus with focal motor seizures of his right arm and leg with aversion of his head to that side. There was secondary generalisation of the seizures. Epileptic activity ceased with intravenous phenytoin and total seizure activity was one

hour without any anoxic episodes. A CT brain scan was normal; no cause for the seizures was evident other than theophylline toxicity. Serum theophylline concentration was 26.7 mg/l. Four months previously on the same dose of aminophylline the serum theophylline was 17.5 mg/l with a serum albumin of 33 g/l. Serum albumin was not recorded at the time of the seizures. He regained consciousness but remained confused; at review one month later both he and his wife complained of the patient's problems with memory. Psychometric testing four months after he was admitted to hospital showed that his IQ was within average range as was verbal fluency. Verbal memory was within the lower range of normal expectation. Visual memory was within the 50th percentile on the copy trial but recall (immediate and delayed) showed swift degradation, scores in both being below the 5th percentile. Learning trials of recall of objects also showed significant deficit and cueing did not aid recall. MRI of the brain showed no abnormality. At present he is unable to carry on his previous work as a self employed insurance broker.

Case 2

A 16 year old girl with asthma and cystic fibrosis developed an exacerbation of her asthma while taking theophylline (500 mg daily), ciprofloxacin, clarithromycin, co-trimoxazole, and flucloxacillin. She had a generalised seizure at home and was admitted to her local hospital 20 minutes later unconscious with upward jerking eye movements. She was cyanosed (PaO₂ 5.28 kPa) and had a further generalised seizure. She was intubated, mechanically ventilated, and treated with intravenous anticonvulsants. She regained consciousness six hours later and was transferred to the regional adult cystic fibrosis centre. Theophylline concentrations were not noted on admission but a routine serum theophylline measurement two months before gave a concentration of 10.8 mg/l. She was noted to be disorientated in time and place and lost her way in the ward. A pronounced deficit in short term memory persisted four months later; she had not yet returned to school. MRI of the brain showed a high signal lesion on the T2 weighted and spin-echo sequences in the left hypothalamus (figure).

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Figure MRI of the brain (in patient 2) (T2 weighted) shows a high signal lesion in the left hypothalamus (arrow). The section of brain is in the axial plane at the level of the inferior aspect of the third ventricle. The left side of the brain is on the right.

Psychometric testing five months after the seizures showed that her IQ was currently within the low to average range. There was a 19 point difference between verbal and performance IQ scores. Verbal fluency was within the high to average range. Verbal memory indicated some deficit being below the appropriate mean at immediate recall and 2SD below the mean at delayed recall. Verbal learning showed slower than expected ability to improve with repeated trials: after five trials performance was 2SD below the peer mean. Visual memory was within the 60th percentile on copy trial but recall scores for both immediate and delayed recall were at the 5th percentile.

Discussion

Both patients developed an amnesic syndrome after seizures associated with theophylline. The anterograde amnesia was the main complaint and the chief disability making them unable to carry on with their pre-morbid occupation. Neuropsychological assessment confirmed the presence of memory impairment in both patients and indicated that they were capable of performing a wider range of tests at levels congruent with their ages and educational levels.

Anterograde amnesia implies either bilateral lesions of the hippocampus, amygdala, or their projections or a lesion involving the septal region, the mamillothalamic tracts, or the dorsomedial nuclei of the thalami. The MRI scan in patient 2 showed a lesion in the left hypothalamus; other than this evidence it was impossible to localise the lesions responsible more accurately. It is proposed that the lesions causing the anterograde amnesia are due to ischaemic cell change resulting from severe seizure activity involving the limbic system. If severe and prolonged, hypoxia may

result in memory disorders and this may have been a contributory factor in patient 2.⁵

There is increasing evidence that theophylline toxicity may cause seizures that result in cerebral damage. A neuropathological study of five patients, who died after status epilepticus that occurred during theophylline treatment, described lesions in the hippocampus, amygdala, and thalamus, especially the dorsomedial nuclei.⁴

Theophylline may cause cerebral damage during seizures by adenosine receptor antagonism.⁶ During seizure activity there is an increase in cerebral blood flow to cope with the increased metabolic demands of excessive neuronal discharges. Theophylline significantly reduces this hyperaemia and thus may enhance neuronal damage.⁷ Another mechanism for neuronal damage may be the release of endogenous excitotoxic glutamate, which in animals may produce lesions in the hippocampus and thalamus.⁸ After eating contaminated mussels, domoic acid intoxication caused seizures followed by severe anterograde amnesia and bilateral neuronal necrosis in the hippocampus and amygdala; the pathological features were similar to that produced experimentally by the excitotoxic kainic acid.⁹

There are particular clinical factors, some of which were present in our two patients, which may predispose certain patients to develop seizures during theophylline treatment. Advanced age,⁴ pre-existing neurological disease,² a low serum albumin,^{9,10} and the concomitant use of certain antibiotics^{1,11} increase the likelihood of theophylline induced seizures. Low serum albumin, almost certainly a feature in patient 1, results in higher concentrations of circulating free theophylline as 55% to 65% of theophylline is protein bound.¹⁰

Treatment with ciprofloxacin,¹¹ the erythromycin group of antibiotics,¹ and cimetidine¹² will cause a rise in serum theophylline concentration probably by an effect at the cytochrome enzyme systems in the liver. Additionally ciprofloxacin may increase the likelihood of seizure activity by direct inhibition of GABA receptor binding in the brain. There is evidence that the frequency of seizures in adults with cystic fibrosis is increasing and this may be due to intensification of therapy in this group of patients by concurrent treatment with ciprofloxacin and theophylline.¹³

The serum concentration of theophylline is a definite factor in the induction of seizures.¹⁴ Concentrations above 30 mg/l are most likely to induce seizures but mildly toxic (20–30 mg/l) serum concentrations may also induce attacks, even during chronic oral treatment in patients with predisposing disorders.¹⁵ In such patients theophylline concentrations should be monitored often and maintained at the lower end of the therapeutic range.

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