The toxic effects of anticonvulsant drugs in long-term treatment of epilepsy

Sir: The chronic toxic effects of anticonvulsant drugs pose considerable problems in the long term treatment of epilepsy.¹ Intellectual deterioration and other mental state changes are probably the most easily overlooked of these toxic effects, especially when not associated with other signs of toxicity.² We report the case of a 45 year old female with temporal lobe epilepsy, who developed overt psychiatric illness after 16 years of treatment with primidone and phenytoin which resolved dramatically on withdrawal of these drugs.

The patient has had temporal lobe absence seizures since the age of 14. She was first seen by a neurologist in 1972, at the age of 29, and therapy with phenytoin and phenobarbitone was started. Primidone was substituted for phenobarbitone in 1974 to achieve better seizure control. Around this time she developed a major depressive episode and was treated with imipramine for a few weeks. She became pregnant in 1980, while on 100 mg tds of phenytoin and 250 mg tds of primidone. Seizure control was particularly difficult during and soon after her pregnancy. Personality changes, which are described below, were first noticed at this time. A moderate degree of depression also developed, and persisted. She complained of 'odd sensations' in her legs and hands in mid 1987. On neurological examination no abnormality, other than a subjective decrease in touch sensation over all fingers, was noted. Serum anticonvulsant levels measured in August 1987 were: phenobarbitone 180.6 micromol/l ('therapeutic range' 64-150.5 micromol/l), phenytoin 67.15 micromol/l ('therapeutic range' 39-79 micromol/l), primidone 46 micromol/l ('therapeutic range' 32-46 micromol/l). Over the years her serum phenobarbitone levels had been maintained at 17-35 micromol/l above the upper limit of the normal range. However, her serum phenytoin and primidone levels were always within normal limits. Throughout this period and until her current admission she was maintained on Phenytoin 100 mg tds and primidone 250 mg tds. She failed to keep outpatient appointments after November 1987.

In May 1988 she returned to work in a bank after a break of 18 years. Within days she began to feel persecuted by her colleagues and felt she was being observed and recorded. She heard the porter's voice saying derogatory things to her when he was not actually present, and also heard strange voices saying "The Wend, wonder when".

She was convinced that a colleague was "setting up something" for her, when she was in fact making an innocent telephone call to her policeman husband. While returning from Ireland she felt that two men on the flight had been sent by the bank to spy on her, and was convinced she could hear them saying "I'm afraid it is a stalemate". She was dismissed from the bank in July 1988 but her symptoms persisted. She thought her neighbours were plotting against her and that felt that something odd was going on, but could not describe this feeling further. She appeared more depressed than usual to her family and was often tearful. She was considerably disabled by her symptoms and was unable to cook, go out alone or take adequate care of her children. Her husband felt she had changed over the past seven years from a vivacious, gregarious, confident person to a withdrawn, sensitive person with poor self-confidence and self-esteem. He was also deeply concerned about the new "psychotic" symptoms which had appeared in recent months.

She was referred to us in August 1988. On examination there was a mild coarsening of features, hirsutism, gingival hypertrophy and horizontal nystagmus. She complained of paraesthesiae on her face, fingertips, lower legs and feet and on clinical examination there was a subjective decrease in fine touch only, over her arms and legs. There was no ataxia. She continued to experience the symptoms outlined above and was extremely tense and paranoid. No cognitive deficits were found. Serum anticonvulsant levels were: phenobarbitone 197.8 micromol/l, phenytoin 83 micromol/l and primidone 46 micromol/l. Other abnormal investigations included an elevated gamma-glutamyl transferase level (91 IU/l), an increased mean corpuscular volume (98.7 fl), moderate, diffuse, non-specific slow wave dysfunction in her EEG and mild cerebellar atrophy on her CT scan (which was also evident on a scan done in 1985). Serum folate was normal (8.4 nmol/l; normal range 5.4-32 nmol/l). She agreed to admission with great reluctance and isolated herself on the ward. She was convinced the staff were "role playing in a specialised game" and was extremely paranoid. She discharged herself within three days but kept outpatient appointments. Soon after re-admission all anticonvulsant drugs were withheld for two days. This brought down the serum anticonvulsant levels to phenobarbitone 142 micromol/l, phenytoin 43.45 micromol/l and primidone 13.8 micromol/l. Phenytoin and primidone dosages were then maintained at 250 mg once daily and carbamazepine 200 mg tds

was started simultaneously. Three days later serum anticonvulsant levels were: phenobarbitone 120.4 micromol/l, phenytoin 39.5 micromol/l and primidone 41.4 micromol/l. By this time all her psychotic features had disappeared completely and she was considerably less depressed. Her depression cleared completely within a week. Phenytoin was withdrawn in steps of 75 mg over three weeks. Primidone was then decreased in steps of 75 mg over three weeks to a dose of 25 mg daily. This was maintained for a month and then stopped. Her paraesthesiae disappeared within six weeks of the initial reduction in dosage. When last seen, on the 30th of November 1988, she remained free of any depressive or psychotic symptoms, with reasonable seizure control on carbamazepine 200 mg tds.

Reynolds and Travers³ studied 118 epileptic patients on various combinations of phenytoin, phenobarbitone and primidone. They found that patients with psychiatric illness, personality changes, intellectual deterioration and psychomotor slowing had significantly higher serum anticonvulsant levels compared with patients without these symptoms. Our patient's case clearly demonstrates this and highlights the need for close monitoring, longitudinally, of subtle mental state changes in patients on long term anticonvulsant treatment. Furthermore, the rapid resolution of her symptoms without the need for antidepressant or neuroleptic medication is an important reminder that serum monitoring should be undertaken and the anticonvulsant regime reviewed before starting any specific treatment in mentally unwell epileptic patients.

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