Phenytoin toxicity due to concomitant antituberculosis therapy

A. Walubo, A. Aboo

Isoniazid inhibits the metabolism of phenytoin. Slow acetylators, who comprise roughly 50% of the South African population, are likely to develop clinical and biochemical features of phenytoin toxicity when this drug is given together with antituberculosis therapy. We describe a patient in whom this interaction caused a series of dangerous clinical events. Seventy-four per cent of patients with epileptogenic disorders seen at the Emergency Unit at Groote Schuur Hospital were on phenytoin and 11.6% of these had blood levels in the toxic range. The wide use of phenytoin during the recent tuberculosis epidemic makes it imperative to suspect this drug interaction in patients exhibiting clinical features that might be related to phenytoin toxicity. Knowledge of this interaction and adjustment of the dose of phenytoin should enable clinicians to avoid this adverse drug interaction.

Phenytoin is widely used as an anti-epileptic agent, as it is effective against generalised and partial tonic-clonic seizures. It is metabolised in the liver mainly by parahydroxylation, a process exhibiting enzyme saturation kinetics and polymorphism at therapeutic concentrations. Isoniazid (INH) inhibits the parahydroxylation of phenytoin, a rate-limiting step in phenytoin metabolism; in some people, this leads to elevation of the plasma phenytoin concentration. Eleven per cent of patients on concurrent therapy with phenytoin and INH exhibited this interaction when on phenytoin 300 mg daily, and all were slow acetylators.

Case summary

A 51-year-old man who had been on phenytoin 300 mg daily for 10 years was started on INH 300 mg, rifampicin 450 mg, pyrazinamide 1 000 mg and ethambutol 800 mg daily for pulmonary tuberculosis on 1 March 1993. Ten days later he presented to the Emergency Unit, Groote Schuur Hospital, with a 2-day history of convulsions.

He frequently used alcohol and was a smoker. The plasma phenytoin concentration was 69 μmol/l (therapeutic range 40 - 80 μmol/l). He was treated with clonazepam 1 mg and discharged on phenytoin 300 mg daily.

Fourteen days later he returned to the Emergency Unit with what his wife described as uncontrollable behaviour. On examination he was restless, confused, disorientated, severely ataxic and hallucinating. The lower lip was swollen, due to an injury incurred in a fall. Intravenous diazepam 10 mg was administered. This sedated the patient and controlled the symptoms. The plasma phenytoin concentration was 238 μmol/l.

He was maintained on clonazepam 1 mg 8-hourly. Antituberculosis drugs were withheld for 2 days and his plasma phenytoin concentration was monitored daily at 10h30 (Fig. 1).

On 26 March (day 2), when the phenytoin level was 142 μmol/l, antituberculosis drugs, excluding ethambutol, were reintroduced. On the following day the phenytoin concentration had risen to 174 μmol/l and the patient was again restless and confused. The aspartate aminotransferase level was 51 IU/l (4 - 36 IU/l), alanine aminotransferase level 55 IU/l (0 - 40 IU/l) alkaline phosphatase 261 IU/l (40 - 120 IU/l) and gammaglutamyl transferase level > 1 500 IU/l (10 - 50 IU/l). Bilirubin, total protein, albumin and electrolyte values were normal.

At this stage the antituberculosis drugs and clonazepam were withdrawn. The patient's condition improved as the phenytoin level decreased. He was discharged on antituberculosis therapy and phenytoin 200 mg daily and was to be followed up at a local day hospital.

Two weeks later our team made a home visit on the same day that he had attended the day hospital. He complained of having had a fit twice in the previous 2 days. He had been given an injection at the hospital and the phenytoin dose had been increased to 300 mg daily. It was learned that he had run out of his antituberculosis medication 4 days before the onset of convulsions and was waiting to obtain new supplies from the tuberculosis clinic the following week.
He was taken to the clinic where antituberculosis medicines were dispensed and the phenytoin dose was adjusted to 200 mg daily. Liver function results had returned to normal.

On the second visit, 1 month later, he was doing well.

Discussion

A mean (± SD) of 73 ± 13 patients per month with epileptogenic disorders were seen in the Emergency Unit of Groote Schuur Hospital during the 6-month period from October 1992 to March 1993. During the same period, plasma phenytoin levels were measured in 54 ± 10 patients per month (74%) and 11,61 ± 6,97% of these were in the toxic range (> 110 mmol/l). Overall, a total of 221 ± 44 patients per month from the hospital had their plasma phenytoin levels measured and 10,02 ± 2,57% were in the toxic range.

Since tuberculosis infection and epileptogenic disorders necessitating phenytoin therapy are endemic in southern Africa, approximately 50% of whose population are slow acetylators, there are likely to be a large number of susceptible people on concurrent therapy with phenytoin and antituberculosis drugs. Our report illustrates how this interaction may occur in these circumstances and how it can be prevented by adjustment of the dose of phenytoin and monitoring of plasma levels of this compound until a new steady state is established.

The authors wish to thank the staff of Groote Schuur Hospital, especially the Department of Pharmacology and the Emergency Unit for their support in preparing this report. A. Walubo is a recipient of the UCT Foreign Students’ Postgraduate Scholarship Award.

REFERENCES


Accepted 3 June 1993.

The value of an elimination diet in the management of patients with ulcerative colitis

S. Candy, G. Borok, J. P. Wright, V. Boniface, R. Goodman

Debate exists about the role of diet in both the aetiology and the management of ulcerative colitis. To examine the latter, a group of patients with documented ulcerative colitis was studied at the Groote Schuur Hospital Gastrointestinal Clinic.

A total of 18 subjects, 9 female and 9 male, were randomised into active or control groups and followed up weekly for 6 weeks. Subjects in the control group were asked to document but not alter their intake of food and drink. Those in the experimental group had their diets systematically manipulated to exclude foods that appeared to provoke symptoms. The symptoms, sigmoidoscopy and biopsy findings of all subjects were compared before and after. 'Remission' was defined as the passage of normal stools with absence of rectal bleeding. 'Improvement' was defined as a decrease in the number of diarrhoeal stools and/or a diminution of rectal bleeding.

At the end of the trial the diet group displayed significantly fewer symptoms than did the controls (P = 0.008; Fisher's exact test). Sigmoidoscopic findings improved in 8 subjects in the diet group compared with 2 of the controls. Histological findings improved in 3 of the diet group as well as in 3 of the controls.

There were no foods that provoked symptoms in all patients, though spiced and curried foods and fruits, especially grapes, melon and the citruses, commonly caused diarrhea. In only 2 patients were symptoms reproduced consistently on reintroduction of a particular food, pork in 1 case and yellow cheese in another.