

# Phenytoin toxicity due to concomitant anti-tuberculosis therapy

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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.

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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,<sup>1</sup> 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,<sup>1-4</sup> 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  $\mu\text{mol/l}$  (therapeutic range 40 - 80  $\mu\text{mol/l}$ ). 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  $\mu\text{mol/l}$ .

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).

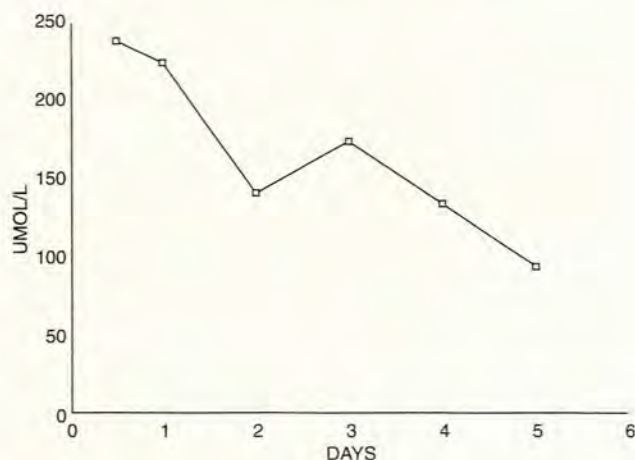


Fig. 1. Plasma profile of phenytoin during the 5 days' stay in hospital.

On 26 March (day 2), when the phenytoin level was 142  $\mu\text{mol/l}$ , antituberculosis drugs, excluding ethambutol, were reintroduced. On the following day the phenytoin concentration had risen to 174  $\mu\text{mol/l}$  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.

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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 ( $\pm$  SD) of  $73 \pm 13$  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  $54 \pm 10$  patients per month (74%) and  $11,61 \pm 6,97\%$  of these were in the toxic range ( $> 110$  mmol/l). Overall, a total of  $221 \pm 44$  patients per month from the hospital had their plasma phenytoin levels measured and  $10,02 \pm 2,57\%$  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.

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