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Phenytoin toxicity associated with hypoalbuminaemia and the paradoxical elevation of serum concentration

Phenytoin, one of the most widely used anti-epileptic drugs, has a narrow therapeutic range because of nonlinear pharmacokinetics. Serum albumin levels also alter serum concentrations of phenytoin because phenytoin is primarily bound to serum albumin (1). Here we report a patient who developed phenytoin toxicity associated with hypoalbuminaemia because of physical complications and the paradoxical elevation of serum concentration.

A 64-year-old woman was transferred from a psychiatric hospital to our university hospital because of repeated cholecystitis. She suffered from severe mental retardation. She experienced generalised tonic–clonic seizures for the first time at 9 years of age. Since then, she has suffered from epilepsy and taken phenytoin in combination with sodium valproate. Daily doses of phenytoin and sodium valproate were 250 and 400 mg, respectively. Drug compliance was good and the total serum phenytoin and sodium valproate concentrations were 12.5 and 46.8 μg/ml, respectively (Fig. 1). Her serum albumin was 3.1 g/dl at the time of admission.

Her body temperature was 38.0 °C and serum alkaline phosphatase was 1300 IU/l. Her diet was stopped and peripheral infusion was started, but oral phenytoin and sodium valproate continued. Treatment with antibiotics, i.e. ceftazidime hydrate 1200 mg for 5 days, clindamycin 2000 mg for 4 days and pazufloxacin mesilate 1000 mg for 17 days, resolved cholecystitis. Unexpectedly, generalised seizures occurred twice during fasting. Her serum albumin decreased to 2.1 g/dl. Surprisingly, the total serum phenytoin concentration increased, so we started to taper off phenytoin dosage. However, the serum phenytoin concentration did not decrease during the following 6 days (maximum 29.7 μg/ml). Intravenous hyperalimentation started and hypoalbuminaemia improved to 3.5 g/dl. Thereafter, total serum phenytoin concentration decreased and her generalised seizures were controlled.

In the present case, seizures were coincident with toxic concentrations of phenytoin in serum (2). However, this toxicity appeared although the dose of phenytoin decreased. It appeared to be a matter of neither absorption nor excretion, because the concentrations of serum valproate did not change. The metabolism of phenytoin is associated with CYP2C9 and CYP2C19 (3). Meanwhile, the metabolism of clindamycin is associated with CYP2A4 (4) and the metabolism of ceftazidime hydrate and pazufloxacin mesilate is not associated with any CYP (5). Thus, the phenytoin toxicity did not appear to be a matter of metabolic interactions.

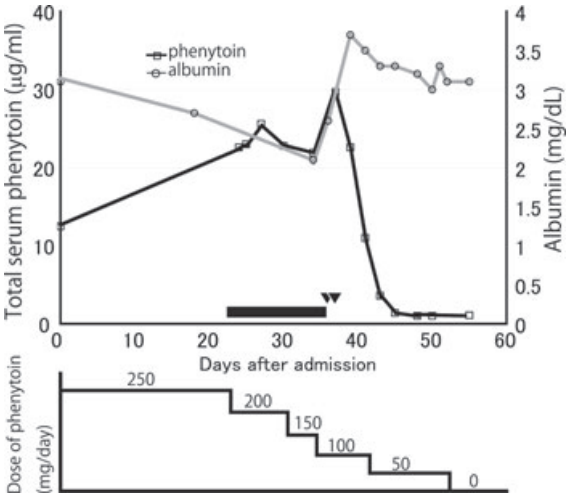

Fig. 1. Clinical course. ○, serum albumin (g/dl); □, serum concentration of phenytoin (μg/ml); ■, duration of somnolence and ▼, occurrence of seizure.

In the present case, phenytoin toxicity occurred with a decrease in the serum albumin concentration probably associated with inflammation and fasting (6) and disappeared after hypoalbuminaemia was resolved.

Another point was the increase in the total serum concentration of phenytoin despite the reduction of phenytoin. Previously, it has also been reported that some of the nine reported cases of phenytoin toxicity showed the elevation of serum phenytoin concentration until 5 days after the cessation of phenytoin (7). It is known that the delay of metabolism is caused by endogenous factors such as inflammation (8) and environmental factors such as fasting and dietary protein. In such cases, the half-life of the drug increases markedly and patients quickly develop symptoms of toxicity. Another possible explanation is that a large amount of phenytoin accumulated in tissues and erythrocytes because of intoxication might have returned rapidly to the serum after reduction of the phenytoin dose (9).

We reported a case with phenytoin toxicity because of hypoalbuminaemia and probable metabolic delay.

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