

Phenytoin toxicity

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DESCRIPTION

A teenage girl, who had been treated with phenytoin sodium for seizure disorder since she was 4 years old, presented with failure to gain height and progressive bowing of her legs for the preceding 3 years. She had received adequate sun exposure and milk intake. She had been treated with oral cholecalciferol (60 000 U/week) for 8 weeks about a year before her presentation to us. Clinical examination revealed gingival hypertrophy (figure 1A), short-limb dwarfism, genu valgum (figure 1B), dry coarse skin and delayed relaxation of the Achilles reflex. Laboratory investigations documented low 25-hydroxy vitamin D (25-OHD) (6 ng/ml) and central hypothyroidism (free thyroxine (T4) 0.72 ng/dl (reference 0.86–1.4 ng/dL); thyroid stimulating hormone (TSH) 0.37 μ IU/mL (reference 0.4–4.27 μ IU/mL)). Radiography showed fraying of metaphyses consistent with rickets (figure 1C). MRI of the brain revealed normal hypothalamo-pituitary region and cerebellar atrophy (figure 1D). Serum phenytoin level was elevated (39 mg/L (reference 10–20 mg/L)). Levetiracetam and levothyroxine were initiated, and phenytoin was gradually withdrawn. The patient was also treated with pulse



Figure 1 (A) Gingival hypertrophy. (B) Genu valgum. (C) X-ray of the knees suggestive of rickets. (D) T1-weighted non-contrast MRI showing normal hypothalamo-pituitary area and cerebellar atrophy (white arrow).

oral cholecalciferol followed by daily cholecalciferol and calcium. Repeat imaging revealed healing lines at the involved metaphyses. Levothyroxine

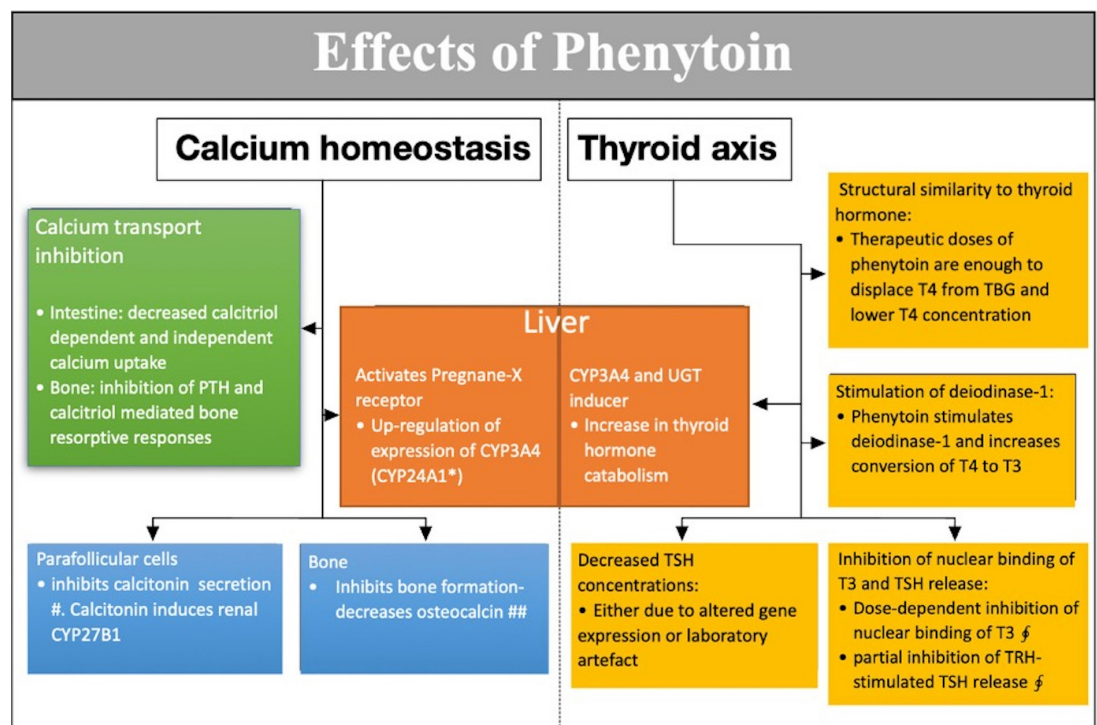


Figure 2 Effects of phenytoin on calcium and thyroid hormone homeostasis. CYP24A1, gene encoding 24-hydroxylase; CYP27B1, gene encoding 1 α -hydroxylase; PTH, parathyroid hormone; TBG, thyroxine binding globulin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone. *Conflicting reports regarding induction of CYP24A1. #Experimental rat model. ##Rat model. ϕ In vitro cultured rat anterior pituitary cells. The figure has been created by Avivar Awasthi, one of the co-authors.



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Table 1 Summary of clinical and biochemical signs of phenytoin toxicity

Clinical signs of toxicity	
Organ system involved	Manifestations
Cerebellum	<ul style="list-style-type: none"> ▶ Nystagmus ▶ Ataxia ▶ Slurred speech ▶ Cerebellar atrophy
Central nervous system	<ul style="list-style-type: none"> ▶ Behavioural changes ▶ Increased seizure activity (hypocalcaemia induced) ▶ Lethargy and confusion ▶ Coma
Cutaneous/mucocutaneous	<ul style="list-style-type: none"> ▶ Maculopapular exanthema ▶ Hirsutism ▶ Toxic epidermal necrolysis ▶ Stevens-Johnson syndrome ▶ Erythroderma ▶ Leukocytoclastic vasculitis ▶ Fixed drug eruptions ▶ Angioedema ▶ Pseudolymphoma ▶ Gingival hypertrophy
Endocrine system	<ul style="list-style-type: none"> ▶ Hypothyroidism ▶ Decreased bone mineral density ▶ Rickets/osteomalacia ▶ Male hyposexuality and sperm dysmotility
Gastrointestinal system	<ul style="list-style-type: none"> ▶ Ageusia ▶ Nausea ▶ Dysphagia ▶ Heartburn ▶ Constipation ▶ Diarrhoea
Biochemical signs of toxicity	
<ul style="list-style-type: none"> ▶ Megaloblastic anaemia ▶ Aplastic anaemia ▶ Elevated ALT, AST, ALP ▶ Hypocalcaemia ▶ Altered TFT ▶ Hyperglycaemia ▶ Increased SHBG 	
<small>ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; SHBG, sex hormone binding globulin; TFT, thyroid function test.</small>	

supplementation was subsequently withdrawn and the girl remained euthyroid.

Phenytoin has a narrow therapeutic index and adversely affects multiple organ systems (table 1). Due to its long half-life, it may be administered in a less frequent daily dosage. It follows non-linear pharmacokinetics; hence, a small increment in dose above the required maintenance dose often results in side effects.

Phenytoin induces gingival hypertrophy, causes cerebellar atrophy, and alters vitamin D and thyroid hormone (TH) homeostasis (figure 2, illustrated by AA, one of the authors).¹ The association between long-term anticonvulsant therapy and rickets/osteomalacia was first described back in the 1960s. Phenytoin interferes with vitamin D metabolism at multiple steps. It enhances hepatic catabolism and subsequent excretion of both 25-OHD and 1,25-dihydroxy vitamin D (1,25-OH₂D) by upregulating 24-hydroxylase expression. It also induces target organ resistance to active 1,25-OH₂D. Moreover, it inhibits calcitonin secretion and thereby reduces calcitonin-induced enhanced renal 1- α hydroxylase activity. Furthermore, phenytoin decreases intestinal calcium and phosphate absorption and decreases osteocalcin; thus, it adversely affects bone health. Though clinically overt bone disease is relatively rare, radiological changes and biochemical alterations are detected in up to 50% and 70% of cases, respectively, with long-term anticonvulsant use—phenytoin, phenobarbitone and primidone in particular. The risk factors for anticonvulsant-induced bone disease are duration of treatment, combination therapy, decreased dietary vitamin D, limited exposure to sunlight, and reduced physical activity.²

Box 1 Recommendations for monitoring of patients being treated with phenytoin^{3 4}

- ▶ Recommended daily dose is 4–7 mg/kg and 300–400 mg in children and adults, respectively
- ▶ Routine monitoring of the serum phenytoin level is not recommended
- ▶ In clinical suspicion of drug toxicity or poor adherence to therapy or uncontrolled seizures, serum phenytoin levels should be measured
- ▶ Therapeutic range is defined as between 10–20 mg/L. However, phenytoin exhibits inter-individual variation
- ▶ In the presence of renal impairment or hypoalbuminaemia, measurement of free phenytoin level should be preferred
- ▶ If free phenytoin concentration is not available then adjusted total concentration may be determined
- ▶ Dose adjustment should not be decided by serum level alone; clinical judgement should also be applied
- ▶ At present, limited evidence exists regarding the reference range of serum phenytoin in paediatric age groups
- ▶ Routine assessment of complete blood count and liver function test is not recommended in asymptomatic individuals

Learning points

- ▶ Phenytoin, a drug with a narrow therapeutic index, is associated with significant systemic toxicity when used in higher dosage and/or for a prolonged period.
- ▶ Phenytoin adversely affects bone health, and growing children exposed to a higher cumulative dose of phenytoin are prone to develop rickets and osteomalacia.
- ▶ Other systemic manifestations of phenytoin toxicity, such as gingival hyperplasia, cerebellar atrophy and alteration in thyroid function tests, should be meticulously searched for in every such case.
- ▶ Early diagnosis of such toxicities and switching to an antiepileptic agent of another class is associated with complete reversal of many of these adverse effects.

Phenytoin shares structural similarities with T4. It displaces T4 from the binding proteins, increases TH catabolism by inducing hepatic microsomal enzymes, stimulates type 1 deiodinase, and inhibits nuclear binding of liothyronine (T3). In addition, it inhibits thyrotropin-releasing hormone-stimulated TSH release leading to a decrease in circulatory TSH. Total and free TH concentrations are often decreased, suggesting central hypothyroidism, as seen in this patient. Phenytoin is known to cause diffuse atrophy of the Purkinje cells of the cerebellum, and the atrophic change correlates with dose and duration of therapy.

Long-term phenytoin therapy often leads to a plethora of adverse effects. Physicians should be aware of such toxic features because replacing phenytoin with another antiepileptic agent often reverses many of these complications. Recommendations for monitoring of patients being treated with phenytoin are summarised in box 1.

Contributors AA, NA, PPC and AM were involved in the diagnosis and management of the patient. AA and PPC did the literature search and wrote the manuscript.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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