

Fatal phenytoin-induced thrombocytopenia in a neurosurgical patient

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EDITOR:

A 66-yr-old female was admitted for scheduled resection of an intracranial tumour. Her medical history included hypertension and diabetes, for which long-term amlodipine and metformin were prescribed. On admission, phenytoin 300 mg once daily and dexamethasone 4 mg 6-hourly were started for seizure prophylaxis. She received neither thromboprophylactic agents nor gastrointestinal protective agents preoperatively. Preoperative full blood count, clotting screen and renal function were normal. Her platelet count was $186 \times 10^9 \text{ L}^{-1}$. Five days after receiving the first dose of phenytoin, she underwent a left fronto-temporal craniotomy with excision of tumour, a meningioma on histology. Anaesthesia, surgery and recovery were all uneventful. Four hours after the operation, her Glasgow Coma Scale (GCS) score dropped acutely to 6/15. An urgent computed tomography (CT) head scan revealed a left-sided intracranial haemorrhage at the operative site, oedema and midline shift greater than 1 cm. She was taken back to the theatre for removal of a bone flap and then transferred to our ICU. Blood investigations sent during this second operation revealed a platelet count of $2 \times 10^9 \text{ L}^{-1}$ and a haemoglobin level of 8.9 g dL^{-1} , with normal clotting screen and renal function. The cause of the severe thrombocytopenia was considered by exclusion to be phenytoin induced. The phenytoin was stopped and platelet transfusions were given, aiming for a count greater than $80 \times 10^9 \text{ L}^{-1}$ to prevent further haemorrhage. In ICU, the patient received ventilatory support and medical treatment for raised intracranial pressure but had a persistent GCS score of 3/15 off sedation. By the third day after stopping the phenytoin, the platelet count was maintained at over $80 \times 10^9 \text{ L}^{-1}$ and there was no requirement for further platelet transfusion (Fig. 1). A further CT head scan performed on this day revealed a large area of haemorrhage deep to the left craniectomy with parenchymal extrusion, considerable mass effect and evidence of ischaemic damage in the frontal, parietal

and occipital lobes. She died from brainstem compression on the fifth day after surgery.

In addition to its use in established seizure disorders, phenytoin is a drug commonly used as a prophylactic agent against seizures in patients with central nervous system tumours and head trauma. Reported haematological adverse effects are uncommon and include lymphadenopathy, megaloblastic anaemia, lymphoma formation, aplastic anaemia, agranulocytosis and isolated thrombocytopenia [1]. The differential diagnosis for isolated thrombocytopenia includes drug-induced, infections, disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, systemic lupus erythematosus and thrombotic thrombocytopenic purpura. We are confident that this case was phenytoin induced as phenytoin and dexamethasone were the only new drugs started before surgery, and the other differentials can be excluded from the medical history and blood tests performed. The time course of recovery of the platelet counts, after discontinuation of phenytoin, also makes it a logical candidate for cause.

Phenytoin-induced thrombocytopenia usually occurs within 1–3 weeks after drug initiation [2–4], but has been detected as early as 2 days and as late as 2 years after starting phenytoin. In our patient, severe thrombocytopenia with a platelet count of $2 \times 10^9 \text{ L}^{-1}$ was detected 6 days after drug initiation.

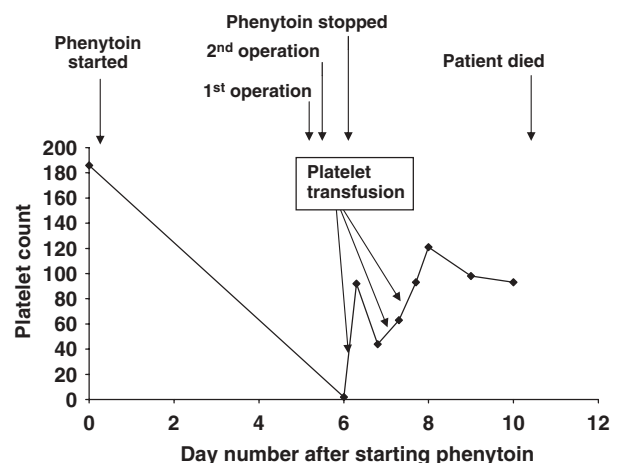


Figure 1. Platelet count $\times 10^9 \text{ L}^{-1}$ on day number after starting phenytoin.

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Initially, selective bone marrow depression was thought to be the responsible mechanism [5], but, after phenytoin-dependent antiplatelet antibodies were demonstrated, an immune-mediated destructive process was deemed more likely [4]. It has been postulated that the epoxide metabolite of phenytoin covalently binds to platelet walls, inducing antiplatelet antibodies against the hapten created, leading to destruction of circulating platelets [6]. The necessary metabolism of phenytoin to phenytoin epoxide, platelet binding and subsequent immune response would account for the delay in onset of thrombocytopenia. Low concentrations of epoxide hydrolase, the enzyme responsible for the breakdown of phenytoin epoxide, would potentially predispose patients to phenytoin-induced thrombocytopenia, on top of those unknown factors that contribute to idiosyncratic reactions. Interestingly, it has been demonstrated that dexamethasone can induce certain hepatic cytochrome p450 enzymes, but inhibits epoxide hydrolase production, conceivably resulting in an increased concentration of phenytoin epoxide [7]. Other agents that potentially increase the concentration of phenytoin epoxide, and have therefore been implicated as a contributory factor in phenytoin-induced thrombocytopenia, include histamine-2-receptor antagonists [6]. The treatment of phenytoin-induced thrombocytopenia is discontinuation of phenytoin and, if the patient has associated life-threatening haemorrhage, platelet transfusion. Giving 1 g kg^{-1} of intravenous immunoglobulin has been associated with a rapid increase in the platelet count, and should be considered [3].

Although an uncommon complication of treatment, this case highlights that phenytoin-induced

thrombocytopenia can be potentially fatal in neurosurgical patients if undetected before surgery. We recommend that a repeat platelet count be performed on all patients that are started on phenytoin before surgery, especially if it has been prescribed in combination with dexamethasone.

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Anaesthetic management and perioperative monitoring of a patient with narcolepsy

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Narcolepsy, also known as Gélinau syndrome, is a chronic sleep disorder characterized by excessive sleepiness during the day, sleep paralysis, hypna-

gogic hallucinations and cataplexy (sudden loss of muscle tone). Common features are uncontrollable attacks of deep sleep and disturbed nocturnal sleep. We report the anaesthetic management for laparoscopic cholecystectomy of a patient with a long history of narcolepsy.

A 50-yr-old woman (92 kg, 172 cm) suffering from narcolepsy was scheduled for laparoscopic cholecystectomy under general anaesthesia. Narcolepsy was diagnosed 20 years ago, after evaluation in

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