PHENYTOIN-INDUCED SEVERE THROMBOCYTOPAENIA POST DEXAMETHASONE CO-ADMINISTRATION IN A PATIENT WITH INTRACEREBRAL HAEMORRHAGE

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Abstract
Phenytoin is commonly prescribed for the prophylaxis of seizures in neurosurgical patients. A phenytoin-induced serious adverse effect of thrombocytopenia has been reported in the literature. The concurrent use of dexamethasone, another commonly prescribed drug in neurosurgical patients, has been reported to aggravate this adverse haematological effect. We present a report of phenytoin-induced thrombocytopenia in a patient concurrently prescribed with dexamethasone, after an intracerebral haemorrhage secondary to a rupture of an arteriovenous malformation. The thrombocytopenia was noted after two weeks of phenytoin medication. Phenytoin was immediately withheld, and seven units of random donor platelets were transfused. A gradual resolution of thrombocytopenia was observed within a week.

Keywords: Phenytoin, Thrombocytopenia, Rehabilitation, Dexamethasone

Introduction
Phenytoin is commonly prescribed for seizure prophylaxis in neurosurgical patients. The rate of thrombocytopenia with anticonvulsants is 0.9 per 100,000 prescriptions (1). There is a single database report in the literature on phenytoin-induced thrombocytopenia with potentially serious complications, including death, in a small number of patients (2). We report severe phenytoin-induced thrombocytopenia in a patient with an intracerebral haemorrhage (ICH) secondary to a left parietal arteriovenous malformation (AVM) rupture. The patient was on phenytoin and dexamethasone medication concurrently.

Case Report
A 20-year-old lady with no known comorbidities presented to the Emergency Department with complaints of a sudden onset of aphasia, on awakening from sleep, associated with vomiting and weakness of the right side of her body. It was not preceded by a headache, dizziness or blurring of vision. There had been no history of trauma to the head and no symptoms of seizures, shortness of breath or chest pain. The Glasgow Coma Scale (GCS) score on arrival was 11/15, E4V1M6. The blood pressure was 140/80 mmHg. A neurological examination revealed right facial weakness, limb hypotonia, a dense hemiparesis with a Medical Research Council (MRC) grade of 0/5, and a reduced sensation to pinprick in the right upper and lower limbs. The routine blood examinations were all normal, and the platelet count was 223 x 10^9/L. A plain computed tomography (CT) scan of the brain showed a left frontoparietal intraparenchymal haemorrhage, with a mass effect and a midline shift (Figure 1). A CT angiogram (CTA) of the brain and a diagnostic cerebral angiogram revealed a left parietal AVM (Figure 2). The patient was managed conservatively and was started on intravenous phenytoin 100 mg thrice daily for seizure prophylaxis and intravenous dexamethasone 4 mg thrice daily for the control of cerebral oedema and mass effect. Dexamethasone was stopped after a week, and intravenous phenytoin was changed to an oral preparation.

After two weeks, she complained of hematochezia associated with the appearance of petechiae spots all over
the upper limbs and the upper back of her trunk. She was afebrile with no signs of distress, tachypnea, abdominal tenderness, anaemia or limb swelling. Proctoscopy revealed a small bleeding internal haemorrhoid. Laboratory examination showed thrombocytopenia with a platelet count of $47 \times 10^9$/L. The peripheral blood film was suggestive of peripheral destruction of platelets with evidence of thrombocytopenia and large platelets. The normochromic normocytic red blood cells had no fragmented cells. There was a mild leukocytosis with neutrophilia (Figure 3). Other blood investigations were normal: the haemoglobin level, coagulation profile, renal and liver biochemistry. Hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV) antigen/antibody were not detected. She was diagnosed with internal haemorrhoids and phenytoin-induced thrombocytopenia.

**Figure 1:** Non-contrast brain computed tomography (CT) imaging showing the blend sign, which appears as a mixed-density hematoma (a hyperdense region with an adjacent relatively hypodense region) in the left frontoparietal intraparenchymal (arrow head) with mass effect and midline shift to the right (arrow).

**Figure 2:** Brain cerebral angiogram images showing left parietal arteriovenous malformation (arrow).

**Figure 1:** A) Low power view of the peripheral blood film showing severe thrombocytopenia; B) High power view showing a single large platelet (Wrights stain).
Phenytoin was immediately discontinued, and sodium valproate 200 mg twice daily was prescribed instead. Seven units of random donor platelets were transfused over the next two days in view of the severe thrombocytopenia with an increased risk of intracranial bleeding. For the bleeding internal haemorrhoid, she was prescribed with hydrocortisone acetate, rectal suppositories, oral micronised purified flavonoid fraction, oral lactulose and intravenous tranexamic acid. The rectal bleeding stopped after two days. Five days after the platelet transfusions and the discontinuation of the phenytoin prescription, the platelet count had increased to 113 x 10^9/L. The petechiae spots over the limbs and trunk also gradually resolved over the following week. The patient resumed her rehabilitation program a few days after the acute thrombocytopenic episode had settled. She progressed steadily and made a good neurological recovery over three weeks. Five months later, the AVM was successfully excised by the neurosurgeon.

**Discussion**

Thrombocytopenia is defined as a platelet count of less than 150 x 10^9/L. Drug-induced thrombocytopenia can occur from reduced platelet production or accelerated platelet destruction (3). Phenytoin is a common anticonvulsant medication after a spontaneous ICH. Its use had been reported to cause adverse haematologic effects (4), with serious rare blood dyscrasias at a reported rate of 2.7 cases per 100,000 prescriptions (1). The incidence of phenytoin-induced thrombocytopenia is even lower, at 1.1 cases per 100,000 prescriptions (1). In this case report, we highlight the interaction between phenytoin and dexamethasone leading to severe thrombocytopenia that required platelet transfusions. There is little literature on phenytoin-induced severe thrombocytopenia with concurrent dexamethasone, and severe thrombocytopenia with a fatal outcome has been reported in a neurosurgical patient prescribed with phenytoin and dexamethasone (8).

The patient most likely experienced accelerated platelet destruction with thrombocytopenia seen in the peripheral blood film from the co-administration of dexamethasone with phenytoin. Phenytoin is eliminated principally by hepatic microsomal enzymes, specifically CYP2C9 and CYP2C19. The reactive intermediate is the harmful metabolite, epoxide, which is further deactivated by epoxide hydrolase enzymes (9). Dexamethasone causes the inhibition of epoxide hydrolase messenger RNA and its protein expression and therefore alters the clearance of the epoxide (10). The increased level of epoxide metabolite is suspected to cause platelet destruction and lead to thrombocytopenia (10). This theory is supported by other reports in the literature of phenytoin-induced thrombocytopenia with concurrent dexamethasone use (8,9,11).

In our patient, thrombocytopenia was seen after two weeks of phenytoin and one week after stopping the dexamethasone. The delayed onset of thrombocytopenia supported an immune-mediated mechanism of the drug-induced thrombocytopenia. Similar to the previous reports, the platelet level of the patient began to recover within a day or two of stopping phenytoin and transfusing platelets (9,11) and returned to normal values within a week. Another antiepileptic drug (AED), sodium valproate was prescribed. The decision was guided by the preference of the surgeon, the need for an AED, the availability of valproate and its effectiveness. The risk of valproate-induced thrombocytopenia, as with other AEDs, is not negligible (2,12). Levetiracetam is a newer AED to consider, although there are reports on levetiracetam therapy causing severe thrombocytopenia, albeit rarely (13). The platelet counts were monitored very closely in the patient. The platelet counts continued to rise and eventually returned to the baseline. She also showed a neurological recovery and did not have further episodes of thrombocytopenia.

In conclusion, phenytoin-induced thrombocytopenia is a rare but serious haematological complication. It should be recognised early especially in patients with an underlying ICH to prevent the detrimental effect on the brain with worsening of the cerebral haemorrhage. Physicians also need to be alert to the potential complication of phenytoin-induced thrombocytopenia when phenytoin is administered concurrently with drugs such as dexamethasone, that inhibit the clearance of the harmful epoxide metabolite. Since thrombocytopenia is asymptomatic unless severe, closer monitoring with serial full blood counts may be necessary for patients receiving both phenytoin and dexamethasone, to detect early deterioration in the platelet count.

**References**


