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CASE REPORT

Epilepsy therapy using phenytoin reduces leukocytes

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ABSTRACT

Background: Epilepsy is a neurological disorder, and the primary goal of treatment is to eliminate seizures while minimizing the side effects of treatment as much as possible. Phenytoin is one of the main drugs in epilepsy treatment. One of the side effects of phenytoin is that it can reduce the number of leukocytes in the blood, thereby increasing the possibility of infection. The minimum number of white blood cells ever counted due to the effects of phenytoin use is 300/mm^3. **Objective**: This report aims to present a rare case of the side effects of phenytoin. **Case:** a 40-year-old woman with a history of epilepsy, chronic kidney disease, diabetes mellitus, and thrombocytopenia presented with leukopenia was referred to our hospital. She had taken phenytoin for 16 days, and her leukocyte had decreased from 1,700/mm^3 at a previous hospital to 470/mm^3 upon admission to our hospital. After discontinuing phenytoin and witching to valproic acid, her leukocyte gradually increased to 2,210/mm^3, thereby that she was able to recover and return home. **Conclusion:** Phenytoin is an antiepileptic drug that can cause leukopenia due to its immunotoxin effects. However, this leukopenia is reversible and typically asymptomatic.

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Highlights

1. Phenytoin for epilepsy causes many side effects due to its toxicity.
2. The haematological side effect of phenytoin including leukopenia.

BACKGROUND

Epilepsy is a neurological disorder that affects 69 million people worldwide, with 90% of cases occurring in developing countries. The prevalence is particularly high in these regions due to various high-risk factor, including head trauma, perinatal injury and central nervous system (CNS) infections (Espinosa-Jovel et al., 2018). Epilepsy is one of the most common neurological disorders though its exact cause remains unclear (Weinstein, 2015). It can occur at any age, from infancy to adulthood

(Löscher and Klein, 2021), with no known etiology. Some researchers hypothesized that the age of onset may be genetically influenced the incidence (Ellis et al., 2019), with 75% of cases starting in childhood (Weinstein, 2015).

Epilepsy can be treated by the use of antiepileptic drugs (AEDs) for medical treatment, with 75% of patients achieving better outcomes (Espinosa-Jovel et al., 2018). The medical management of epilepsy is lifelong (McCormick, 2001), primarily to eliminate seizures and minimize treatment side effects. The main therapies of choice for treating epileptic seizures are phenytoin, sodium valproate, levetiracetam, lamotrigine, carbamazepine, oxcarbazepine, topiramate, or zonisamide, which are included in AED (Ellis et al., 2019).

Phenytoin is a well-known anticonvulsant used to treat seizures in epilepsy patients (McCormick, 2001). However, it is associated with several adverse effects, such as sedation, dermatitis, non-thrombogenic purpura, tremors, ataxia, and dizziness, due to its toxicity, despite its effectiveness in controlling seizures. In rare cases, phenytoin has been linked to secondary anemia (Finkelman and Arieff, 1942). The toxic effects of phenytoin may be related to increased dosage or the route of administration as the drug is metabolized by the enzyme CYP450 in the liver (Faturachman et al., 2022).

Phenytoin can reduce the number of leukocytes in the blood, increasing the chance of infection, and it may also decrease platelet counts, which are essential for blood clotting. Animal studies in mice have shown that phenytoin reduces circulating neutrophils and lymphocytes, while increasing circulating eosinophils, suggesting suppression of the humoral immune response and delayed type IV hypersensitivity responses (Al-Fararjeh et al., 2013). The minimum white blood cell counts recorded due to phenytoin use is 300/mm^3. Additionally, liver enzyme levels increase. When phenytoin is discontinued, leukopenia and elevated liver enzymes typically resolve (Espinosa-Jovel et al., 2018).

OBJECTIVE

This report aims to present a rare case caused by the side effects of phenytoin.

CASE

At our hospital did a 40-year-old woman with a history of epilepsy presented with leukopenia, chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), and thrombocytopenia complain of vomiting more than four times, a burning sensation in her chest, and itching all over her body with a history of diabetes and epilepsy. Her medication history was that she consumed phenytoin 3 x 100 mg (taken since January 23, 2024, for approximately 16 days), citicoline 3 x 500 mg, piracetam 1 x 800 mg, folic acid 1 x 1mg, vitamin B6 1 x 1 mg and 1x75 mg, atorvastatin 20 mg at night, spironolactone 25 mg 1-0-0, bisoprolol 2.5 mg, and candesartan 0-0-1. Upon examination, her Glasgow Coma Scale (GCS) was 15 (E4V5M6); the blood pressure was 121/87 mmHg; the pulse rate was 98 beats/minute; the respiratory rate (RR) was 20 breathes per minute; and the oxygen saturation (SpO_2) was 98% in the room air. Physical and neurological examination were within normal limits. Supporting test results from a previous hospital (dated February 8, 2024) showed her leukocytes at 1700 /mm^3, hemoglobin (Hb) at 8.6 g/dL, platelets (PLT) at 124,000, aspartate transaminase (SGOT) at 74 U/L, alanine transaminase (SGPT) at 69 U/L, and blood glucose at 178 mg/dL. Laboratory results from RSPAL dr. Ramelan Surabaya (dated February 9, 2024) revealed her leukocytes at 850/mm^3, Hb at 8.00 g/dL, PLT at 139,000, creatinine at 5.9 mg/dL, blood urea nitrogen (BUN) at 69 mg/dL, and HbA1C at 9.0%.

The results of a head CT scan from the previous hospital concluded that there was a subacute cerebral infarction in the cortical and subcortical regions of the right frontal lobe, suspected with right mastoiditis. On the following day, the patient had complete blood count checked again with leukocyte at 690/mm^3, Hb at 9.40, and PLT at 183,000. The therapy remained unchanged on the next day. On the fourth day of treatment, the results showed her leukocytes at 470 /mm^3, Hb at 10.20 g/dl, and PLT at 212,000. At this point, phenytoin was stopped and replaced with Depakote ER 500 mg tab (0-0-1). For seizures, diazepam 1 amp was administered via IV slowly (2-5 minutes) without dilution. After the administration of phenytoin was stopped, leukocytes began to increase to 490/mm^3. The laboratory

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results were re-checked, and they showed that leukocytes had risen again to 630/mm³, Hb 10.20, and PLT 306,000. On the following day, with the same therapy, the results showed her leukocytes at 2,210 /mm³, Hb at 10.9, and PLT at 309,000. After the overall treatment, the patient was then discharged.

DISCUSSION

Phenytoin has side effects on blood cells, including thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression due to its toxicity (Neki and Shah, 2016). Phenytoin is metabolized into arene oxide, which may represent the toxic or immunologic intermediate (Curry et al., 2018)**.** The therapeutic range of phenytoin is narrow, about 10 to 20 mcg/mL. When plasma concentration is below 10 mcg/mL, the liver enzyme CYP450 can eliminate it. However, at higher concentration within the therapeutic range, the metabolic pathway of phenytoin becomes saturated, shifting its elimination by the liver to zero-order kinetics. The toxicity becomes obvious at higher concentrations (above 10-20 mcg/mL), with varying degrees of clinical symptoms (Menon et al., 2015). In diabetic patients, phenytoin may induce hyperglycemia via insulin insensitivity or insulin resistance (IR) (Al-Rubeaan and Ryan, 1991). The adverse effect of phenytoin administration related to blood cells may be due to blood dyscrasia as phenytoin induces severe bone marrow suppression (McCormick, 2001). A case report also described thrombocytopenia due to phenytoin administration via blood dyscrasia. Thus, blood investigation such as complete blood cell (CBC) is also important to detect its toxicity (Gangadaran and Balasubramanian, 2023). The impact of phenytoin on blood parameters has been proven (Çağ et al., 2019). Phenytoin also stimulated bicytopenia and anemia in a 77-year-old woman (Santimaleeworagun et al., 2018). Another case reported phenytoin-induced thrombocytopenia in a 15-year-old boy (Brown and Chun, 1986), as well as aplastic anemia (Bindu et al., 2020), and neutropenia (Salem and El-Bardissy, 2021).

Leukopenia is frequently observed in patients receiving antiepileptic drugs (AEDs), particularly those with more than one drug. Leukopenia is defined as a white blood cell (WBC) count < 4,000/µl (O'Connor et al., 1994), or a reduction of circulating WBC, especially the granulocytes abnormally. The reduction may be due to limited production, increased WBC utilization and/or destruction caused by infection, drugs, malignancy, megaloblastosis, hypersplenism, or immunoneutropenia (Ing, 1984). Phenytoin, which causes leukopenia, is classified as inducing a hypersensitivity reaction to phenytoin, resulting in the formation of toxic metabolites. The mechanisms involved are immune complex antigen-antibody reactions, changes in the function of lymphocytes and neutrophils which cause autoimmunity, and hapten enzyme disorders (Glauser and Loddenkemper, 2013). A study noted that patients receiving AEDs with chronic leukopenia had normocellular bone marrow (i.e., bone marrow did not experience bone marrow suppression), with two subjects experiencing mild relative splenomegaly on liver-spleen scans (not hypersplenism) with normal platelet and red blood cell, and none of the subjects had PMN antibody. Due to this evidence, the researchers suggested that there was antibody-mediated peripheral destruction of WBC as the underlying cause of leukopenia (O'Connor et al., 1994). Based on a study using carbamazepine (CBZ) as AED this drug showed its toxicity toward leukocyte count, lymphocyte count, serum IgA, and IgM levels. Its effect was correlated with the duration of CBZ therapy in children (El-Shimi et al., 2021).

In more detail, this mechanism consists of the hapten mechanism, immune complex mechanism, and autoimmune mechanism. In the hapten mechanism, there is a molecule from the drug or its metabolite that binds to the neutrophil membrane or myeloid precursor which causes the formation of this hapten which induces the destruction process of leukocyte cells. In the immune complex mechanism, antibodies bind to the drug phenytoin which then form an immune complex that causes leukocyte destruction. In the autoimmune mechanism, antibody-induced drugs will react with neutrophils (Weinstein, 2015).

The mechanism of action of phenytoin can occur due to its toxic effects in immunological phenomena (Neki and Shah, 2016), which is mediated by the presence of neutrophil antibodies. The presence of ROS produced by NADPH oxidase and neutrophil myeloperoxidase plays an important role in the phenytoin oxidation process. This ROS formation occurs within a few seconds after neutrophil

stimulation lasts for hours, and it causes the production of hypochlorous acid (HOCI). This hypochlorous acid is the main cause of the oxidation of this drug; hence, it becomes a reactive product that then covalently bonds to form a molecular complex, becoming a hapten that induces the main antibodies to fight neutrophils and neutrophil precursors in the bone marrow. Immune complex, hapten, and autoimmune mechanisms are the three main mechanisms by which drugs induce leukopenia due to the immune system causing cell lysis, leucoagglutinin formation, or reticuloendothelial elimination (Weinstein, 2015).

Reactions mediated by T lymphocytes are also involved, namely the production of perforin and granzyme by cytotoxic T lymphocyte cells which is triggered by large granular lymphocytes. This immunological process is reversible and asymptomatic. Phenytoin which causes severe leukopenia has a rare incidence, but patients who have a history of previous leukopenia should be more alert before using phenytoin drugs.

The primary organ affected by phenytoin is the liver, which is responsible for drug metabolism and elimination and is susceptible to toxicity such as liver injury. Therefore, detecting liver function is important, and the markers are aspartate aminotransferase (AST), alanine aminotransferase (ALT), and cholestasis enzymes like alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) (Neki and Shah, 2016). Phenytoin leads to liver fibrosis due to chronic liver damage (Curry et al., 2018). Cases of liver injury may arise after 2 to 8 weeks of phenytoin therapy, with clinical symptoms such as fever, rash, facial edema, and lymphadenopathy. After a few days of the therapy, jaundice and dark urine are present. These symptoms may include blood abnormalities such as increased WBC and atypical lymphocytosis (Curry et al., 2018). The reference value of SGPT was 10-55 U, and the SGOT value was 10-40 U/L. When the level increases by threefold, the practitioner must be cautious (Hussein et al., 2013).

To reduce the effect of phenytoin, we prescribed the folic acid supplementation. This supplementation resulted in a 62% reduction in health risk such as anemia in the population. Phenytoin and other AEDs tend to lower the folate serum level as they interfere with folate metabolism (Asadi-Pooya, 2015). Moreover, another phenytoin side-effect was neurotoxicity. However, because phenytoin can alter the blood cells, folic acid therapy may lead to macrocytosis and megaloblastic anemia as the response to folic acid therapy (Neki and Shah, 2016).

Limitations

Due to the rarity of the leukopenia prevalence resulting from the side effect of phenytoin, the author only examined one patient in this case.

CONCLUSION

Phenytoin is an antiepileptic drug that can cause leukopenia due to its toxicity in the immune process, and the effect of this leukopenia is reversible and asymptomatic.

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Conflict of Interest

The author declares no conflict of interest.

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Patient Concern for Publication

Informed consent was voluntarily obtained from the patient regarding the dissemination of their case details, upholding their autonomy and privacy rights.

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Author Contribution

The authors contributed to all stages of this report, including preparation, data collection, drafting the manuscript, and approval for the publication of the manuscript.

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