Case Report

Agranulocytosis and Anemia during Treatment of Seizure with Phenytoin

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Abstract:

Phenytoin has been widely used in clinical practice with a good efficacy but its adverse drug reaction is also incessantly reported. A 72-year-old man with lobar hemorrhage at the left parieto-occipital lobe and old ischemic stroke who developed seizure 3 times and phenytoin was used to control meanwhile, his seizure was investigated. After 22 days of phenytoin administration, his complete blood count revealed bicytopenia including white blood cell count of 1.3 x 10^9/L with an absolute neutrophil count of 0.338 x 10^9/L and hemoglobin level of 10.1 g/dL. The bone marrow aspiration and trephine biopsy confirmed markedly decreased of erythroid and myeloid precursors. He was diagnosed with agranulocytosis most likely from phenytoin. Phenytoin was discontinued and substituted by levetiracetam. Filgrastim was also prescribed for neutropenia. Nine days later, he recovered from agranulocytosis without any serious infection.

Keywords : ● *Phenytoin* ● *Agranulocytosis* ● *Anemia*

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รายงานผู้ป่วย

ภาวะแกรนูโลไซต์น้อยและโลหิตจางระหว่างรักษาการชักด้วยเฟนิโทอิน

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บทคัดย่อ

Phenytoin เป็นยากันชักที่ใช้อย่างแพร่หลายในทางคลินิกเนื่องจากมีประสิทธิภาพดี แต่ในขณะเดียวกันก็พบรายงานอาการอันไม่พึงประสงค์จาก phenytoin อย่างต่อเนื่อง ผู้ป่วยชาย อายุ 72 ปี มาด้วยเลือดออกในสมอง ชนิด lobar hemorrhage ที่สมอง parieto-occipital lobe ซีกซ้าย และพบรอยโรคสมองขาดเลือดเดิม ผู้ป่วยมีอาการชัก 3 ครั้ง จึงใช้ phenytoin เพื่อควบคุมภาวะชัก หลังจากใช้ phenytoin เป็นเวลา 22 วัน ผลการตรวจความสมบูรณ์ของเม็ดเลือด (complete blood count) พบภาวะ bicytopenia คือ เม็ดเลือดขาว 1,300 เซลล์/ไมโครลิตร และมี absolute neutrophil count 338 เซลล์/ไมโครลิตร และ ระดับฮีโมโกลบิน 10.1 ก./ดล. ผลการตรวจไขกระดูกพบจำนวน erythroid precursor และ myeloid precursor ลดลงอย่างชัดเจน จึงวินิจฉัยว่ามีภาวะแกรนูโลไซต์น้อย (agranulocytosis) อันเนื่องมาจาก phenytoin มากที่สุด phenytoin จึงถูกเปลี่ยนเป็น levetiracetam เพื่อควบคุมชัก และได้รับ filgrastim เพื่อรักษาภาวะนิวโทรฟิลต่ำ หลังจากนั้น 9 วัน ผู้ป่วยก็ฟื้นตัวจากภาวะแกรนูโลไซต์น้อยโดยไม่มีภาวะติดเชื้อรุนแรง

คำสำคัญ : ● *Phenytoin* ● *Agranulocytosis* ● *Anemia*

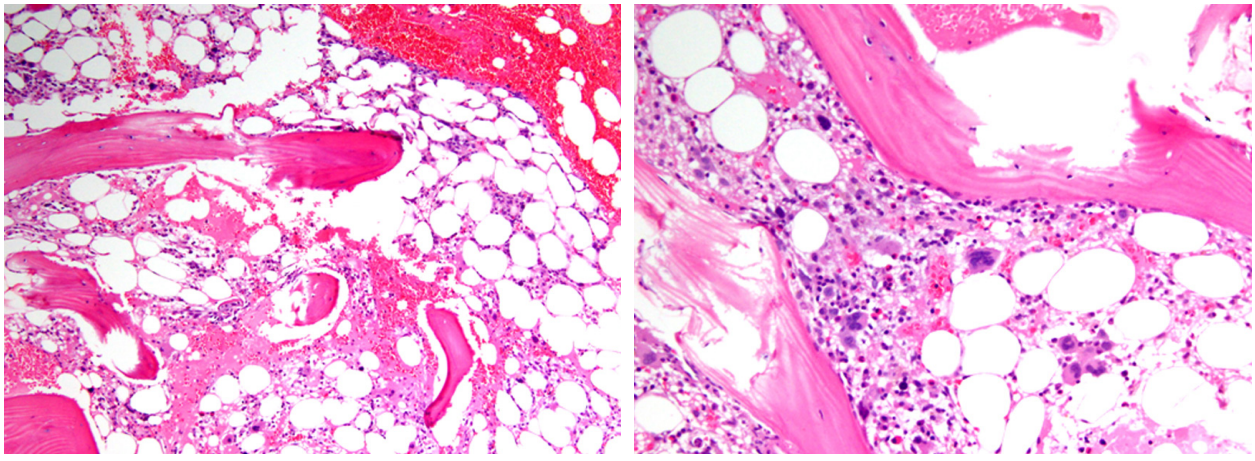
วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2561;28:295-9.

Introduction

Phenytoin (diphenylhydantoin) was firstly synthesized by Heinrich Biltz in 1902[1]. Since 1938, phenytoin has been widely used in clinical practice. It blocks the active state of the sodium channel that prolongs its fast inactivated state. This action reduces high-frequency actions that take place during a seizure and then allows normal action potentials to generate. Phenytoin is available as oral and parenteral preparations. Its adverse effects have been reported including ataxia, dysarthria, nystagmus, allergic rash, Stevens-Johnson syndrome, gingival hyperplasia and liver toxicity[2]. This article mainly reports regarding agranulocytosis caused by phenytoin.

Case Report

A 72-year-old man with lobar hemorrhage at the left parieto-occipital lobe and old ischemic stroke at the left middle cerebral artery (MCA) territory, his current medications consist of vitamin B complex, folic acid, atorvastatin and aspirin. He came to the emergency room because he had developed muscle contraction and jerking for a couple of hours. During two hours before hospital arrival, he developed entire body contractions and jerking. After two minutes, these symptoms resolved spontaneously but he developed urine incontinence. Thirty minutes later, he had two more episodes of seizure. His complete blood count showed hemoglobin 14.5 g/dL, hematocrit (Hct) 42.5%, white blood cell count (WBC) 15.5 x 10^9/L with polymorphonuclear (PMN) 68.3% and platelets (Plt) 245 x 10^9/L. His serum electrolyte revealed sodium 137 mEq/L, potassium 3.09 mEq/L, corrected calcium 9.08 mEq/L, phosphate 3.4 mEq/L and magnesium 2.1 mEq/L. His kidney and liver functions were normal. Computed tomography (CT) revealed old hypodensity lesion at the left fronto-parieto-occipital area with hydrocephalus and skull deformity. He was diagnosed with first episode of provoked seizure from an old structural brain lesion. He received diazepam 10 mg intravenously and phenytoin sodium 750 mg intravenous injection over 30 minutes then 100 mg intravenously every 8 hours. The next day, he received ceftriaxone 2 g for 5 days to treat urinary tract infection. On 22nd day of phenytoin use, his complete blood count revealed WBC count 1.3 x 10^9/L, PMN 26%, absolute neutrophil count 0.338 x 10^9/L, hemoglobin 10.1 g/dL and Plt 187 x 10^9/L. On the same day, the bone marrow aspiration and biopsy were performed. The bone marrow smear was aparticulated marrow, the trephine biopsy showed hypocellular marrow with an approximate cellularity of 20%. All hematopoietic elements presented progressive maturation with decreased erythroid and myeloid precursors and normal megakaryocytes. (Figure 1)



A B

Figure 1 Bone marrow biopsy (A.-40x, B.-200x) showing hypocellarity marrow (20%) with reduced erythroid and myeloid precursors. Megakaryocytes were adequate in number and morphology.

Phenytoin was discontinued and substituted by levetiracetam 500 mg every 12 hours. Filgrastim was also simultaneously administered. Seven days later, WBC was start to rise to 2.3 x 10^9/L with PMN 25%. On the ninth day of phenytoin discontinuation, WBC and PMN were 48 x 10^9/L and 72%, respectively, then filgrastim was stopped. Finally, his WBC count remained at 13.3 x 10^9/L with PMN 53%.

Discussion

With the Oxfordshire Community Stroke Project, an increment risk of suffering a post stroke seizure was 0.9% at 1 year and 4.2% at 5 years[3] especially among patients with supratentorial lobar or extensive hemorrhages (15%), followed by subarachnoid hemorrhage (8.5%) and cortical stroke, usually in MCA (6.5%)[4]. Currently, no clear clinical guidelines are available regarding recommending antiepileptic drugs (AED) for the management of poststroke seizures. Unclear issues also include when to start an AED, which is the best AED and appropriate duration of treatment. However, phenytoin was the most common AED for all types of epilepsy or seizure.[5]

Regarding blood dyscrasia, Rawanduzt and colleagues reported phenytoin induced severe bone marrow suppression and agranulocytosis in a 77-year-old woman receiving phenytoin 400 mg daily for seizure prophylaxis. Her initial laboratory results showed WBC 6.9 x 10^9/L, Hct 42% and Plt 272 x 10^9/L. Thirty days after taking phenytoin, she developed fever, headache and cellulitis at the right upper eyelid, right middle finger and right knee joint. The CBC revealed WBC 0.9 x 10^9/L, Hct 32.5%, Plt 87 x 10^9/L and PMN 3%.[6] The onset of phenytoin induced bone marrow suppression was similar to this patient (30 days and 22 days, respectively) but a little difference was our patient showed only bicytopenia of WBC and red blood cell.

Unlike our patient, Sharafuddin and coauthor reported one patient with lung cancer developed agranulocytosis after taking phenytoin 300 mg daily for two weeks. He presented with WBC count 0.3 x 10^9/L with no circulating neutrophils. The other cell series i.e.Hct and Plt were in normal limits. Bone marrow biopsy confirmed the absence of granulocyte precursors. Seven days after discontinuation of phenytoin, peripheral neutrophils were over 0.8 x 10^9/L. This report showed earlier onset than our patient. Only granulocyte precursor was depleted.[7]

Agranulocytosis is defined as a reduction in the number of mature myeloid cells in the blood to a total count of less than 0.5 x 10^9/L. Drug-induced agranulocytosis may result in either parent drug or toxic metabolites or by products. The mechanisms of toxicity are classified into three proposed mechanisms. Regarding the hapten mechanism, a small molecule of a drug such as penicillin, gold or its metabolite binds to the membrane of the neutrophil or myeloid precursor and then antibodies are induced to destroy these cells. For the immune-complex mechanism, antibodies bind to a causative drug then this immune complex binds to the target cell, leading to leukocyte destruction. Quinidine and quinine are the prototypes of this mechanism. Regarding autoimmune mechanism, the drug activates the production of autoantibodies that react with neutrophil.[8] Uetrecht proposed that the mechanisms of phenytoin toxicity resulted from leukocyte toxicity. Phenytoin is oxidatively chlorinated by the myeloperoxidase (MPO)/H_2O/Cl- system to N, N'-dichlorophenytoin that covalently binds to activated neutrophils. The complex is related to hapten-mediated drug reactions.[9]

In summary, the present report showed agranulocytosis and anemia after taking phenytoin for 22 days without other suspected agents. The bone marrow studies confirmed markedly decreased erythroid and myeloid precursors that correlated with a peripheral absolute neutrophil of 0.338 x 10^9/L. The first important management was to stop phenytoin and substituted with other AEDs. The proposed mechanisms of phenytoin-induced agranulocytosis were leukocyte toxicity throughits metabolite binding to activated neutrophil.[9]

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper

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References

1. *Karthikeyan M, Saquib AAK, Karthikeyan D. Therapeutic applications of phenytoin. Asian J Pharm Clin Res. 2009;2:1-14.*
2. *Abou-Khalil BW. Antiepileptic Drugs. Continuum (Minneap Minn). 2016;22(1 Epilepsy):132-56.*
3. *Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. BMJ. 1997;315:1582-7.*
4. *Gilad R. Management of seizures following a stroke: what are the options? Drugs Aging. 2012;29:533-8.*
5. *Garrard J, Harms S, Hardie N, Eberly LE, Nitz N, Bland P, et al. Antiepileptic drug use in nursing home admissions. Ann Neurol. 2003;54:75-85.*
6. *Rawanduzy A, Sarkis A, Rovit RL. Severe phenytoin-induced bone marrow depression and agranulocytosis treated with human recombinant granulocyte-macrophage colony-stimulating factor. Case report. J Neurosurg. 1993;79:121-4.*
7. *Sharafuddin MJ, Spanheimer RG, McClune GL. Phenytoin-induced agranulocytosis: a nonimmunologic idiosyncratic reaction? Acta Haematol. 1991;86:212-3.*
8. *Greene EM, Hagemann TM. Drug-Induced Hematologic Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill Education [Internet]. 2017 [cited 2018 Aug 30]. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146079796.*
9. *Uetrecht J, Zahid N. N-chlorination of phenytoin by myeloperoxidase to a reactive metabolite. Chem Res Toxicol. 1988;1:148-51.*