

CASE REPORT ON PHENOBARBITONE-INDUCED ERYTHEMA MULTIFORME

Sarwamangala S. Nanjayyanamth¹, Nirupama Kulkarni¹, Sanatkumar B. Nyamagoud^{2*}, Usha D. S² AHM Vishwanath Swamy³ and Varsha I. Dalal²

¹Pharm D Interns, Department of Pharmacy Practice, KLE College of Pharmacy, Hubballi. A Constitue Unit of K.L.E Academy of Higher Education and Research, Belagavi, Karnataka, India.

²Assistant Professors, Department of Pharmacy Practice, KLE College of Pharmacy, Hubballi. A Constitue Unit of K.L.E Academy of Higher Education and Research, Belagavi, Karnataka, India.

³Principal, KLE College of Pharmacy, Hubballi. A Constitue Unit of K.L.E Academy of Higher Education and Research, Belagavi, Karnataka, India.

*Corresponding Author: Sanatkumar B. Nyamagoud

Assistant Professor, Department of Pharmacy Practice, KLE College of Pharmacy, Hubballi. A Constitue Unit of K.L.E Academy of Higher Education and Research, Belagavi, Karnataka, INDIA.

Article Received on 24/05/2022

Article Revised on 14/06/2022

Article Accepted on 04/07/2022

ABSTRACT

Phenobarbitone is an anti-epileptic known to cause skin reactions in 1 to 3% of patients. Erythema multiforme is an acute, immune-mediated condition that is a type 4 hypersensitivity reaction that affects the skin and mucous membranes. Here we report a case of phenobarbitone-induced erythema multiforme of a 43-year-old female patient presenting to the hospital with complaints of loss of appetite for 15 days, and fever with chills for 3 days. She has had a medical history of seizures past 1 year and is on medications tablet phenytoin 100mg twice a day and tablet phenobarbitone 60 mg once a day at night. Symptoms intensified on continuing medication and subsided on withdrawal of medication. Hyperpigmentation lesions on the upper and lower limbs and abdomen were observed from 4 to 5 days. Phenobarbitone was discontinued from treatment on 28/4/2022. Since the patient was diagnosed with viral erythematous fever, the rechallenge was risky and life-threatening, dechallenge improved the patient's condition hence based on the criteria of the WHO causality assessment scale, it was revealed as a probable/ likely adverse drug reaction.

KEYWORDS: Phenobarbitone, erythema multiforme, hypersensitivity reactions, WHO causality assessment, adverse drug reaction (ADR).

INTRODUCTION

Phenobarbitone is a barbiturate that was initially used as an anti-epileptic medication in 1912. It contains anticonvulsant effects that are just not entirely dependent on CNS depression. It has revealed quantitative variations in several aspects of the activity [GABA-Mimetic, Anti-glutamate, and so on]. It has a wide spectrum of anticonvulsant properties that help to reduce seizure frequency and spread.^[1]

The main disadvantage of phenobarbitone as an anti-epileptic is its sedative effect; long-term use may result in behavioral abnormalities, intelligence loss, learning and memory impairment, and hyperactivity in children, mental confusion in the elderly, rashes, megaloblastic anemia, and osteomalacia.^[1]

Erythema multiforme is a kind of skin rash that develops as a result of a viral infection. Erythema Multiforme can be caused by medications including barbiturates, NSAIDS, phenothiazines, and sulfonamides, as well as infections like Herpes Simplex Virus, Mycoplasma,

Pneumonia, Influenza, Adenovirus, Hepatitis, and HIV. Erythema multiforme causes itching, burning rashes, a fever of 100 F^o on and off, headache, joint discomfort, coughing, and difficulty breathing. The face, hands, and lower limbs can all be affected by erythema multiforme.^[2]

CASE REPORT

A 42-year-old female patient was admitted to KIMS Hospital Hubballi. She started to show symptoms of loss of appetite from 15 days, and fever with chills for 3 days. She has had a medical history of seizures past 1 year and is on medications tablet phenytoin 100mg twice a day and tablet phenobarbitone 60 mg once a day at night. Symptoms intensified on continuing medication and subsided on withdrawal of medication. Hyperpigmentation lesions on the upper and lower limbs and abdomen were observed from 4 to 5 days. She was admitted to the hospital for further examinations.

On admission, her blood pressure was 110/90 mmHg, pulse rate 96 beats/min, and respiratory rate 18cpm.

Laboratory investigations such as CBC, liver function test, renal function test, thyroid markers, and serum electrolytes were normal.

On local examination, pink color lesions were present over the abdomen, on both upper and lower limbs, which were irregular in size and itching in nature, and a slight rise in temperature.

In view of the above complaints, the patient was referred to the dermatology department for further examination. The dermatologist on examination confirmed as multiple well-defined erythematous maculopapular rashes with few targetoid papules presented over the face and lower limbs, back, and buttock. Few scaly plaques were present over the neck. She was diagnosed with viral erythematous fever, seizure disorder, and drug rash secondary to phenobarbitone.

The patient was treated with two antibiotics that are doxycycline 100mg p/o twice a day, piperacillin and

tazobactam 4.5g IV thrice a day. For erythematous lesions, she was treated with dexamethasone, pheniramine, and cetirizine. Other conservative treatment includes ondansetron, paracetamol, and calamine lotion for the local application twice a day. Phenobarbitone was discontinued from treatment on 28th April 2022. The patient was having a viral erythematous infection that might cause multiple organ dysfunction so the rechallenge was avoided. Therefore, dechallenge that is the withdrawal of the offending drug was done. Hence based on the WHO causality assessment scale, it was reported as a probable/ likely adverse drug reaction.

After the systemic treatment and discontinuation of the phenobarbitone medication, the patient's condition started to resolve. The patient was feeling better at the time of discharge and was advised not to take the phenobarbitone medication. She was asked to review after 2 weeks in the outpatient department of KIMS hospital.



Image 1: Abdomen.



Image 2: Upper limb (Thigh region).



Image 3: Hands.



Image 4: Lower limb (Knee region).

DISCUSSION

Antiepileptic phenobarbitone is reported to induce skin problems in 1 to 3% of individuals. Erythema multiforme is a type 4 hypersensitivity reaction that affects the mucosal surfaces. It is an acute, immune-mediated condition. On the surface of the membrane of basal epithelial cells lies a protein termed the major histocompatibility complex (MHC class 1 molecule). This protein transports peptides from inside cells to immune cells known as cytotoxic T cells, which detect the peptides as foreign (for example, virally infected cells) and destroys the presenting cell.^[3] In this case, the patient tested positive for the Widal and Weil Felix tests, indicating the presence of virogens. As a result, an immune-mediated response occurred, recognizing viral peptides as a foreign substance.

Erythema multiforme, as the name implies, comes in a range of forms and sizes. Macules (flat red or pink patches), vesicles (small raised fluid-filled lesions), bullae (big raised fluid-filled lesions), and papules (large raised fluid-filled lesions) are all examples of papules (solid elevations containing no fluid).^[4] Targetoid lesions, which range in size from 2mm to 2cm and contain central epidermal necrosis surrounded by concentric rings of erythema, like a bull's eye or target, are the most common of all lesions.^[5] The presence of a maculopapular rash with targetoid papules may be seen in this instance. These presenting symptoms are classified as minor in the erythema multiforme classification. Histologically, there are few lymphocytes near the dermo-epidermal junction. Over time inflammatory cells come to the area and are seen around blood vessels. Basal epithelial cells start undergoing necrosis and subepithelial and intraepithelial vesicles start to appear.

IV rehydration and pain control are used to treat these presenting symptoms. The offending drug (phenobarbitone) must be discontinued. If an infection is confirmed, antibiotics are the first line of defense, followed by the use of systemic corticosteroids to aid in the reduction of inflammation. Although the erythema multiforme caused by Herpes Simplex Virus (HSV) usually fades on its own within a week, continual oral acyclovir might be utilized if the symptoms of erythema multiforme persist (add ref). In this situation, the patient was given doxycycline for rickettsia infection and piperacillin antibiotic for widal positive for a period of 5 days. To control and minimize inflammation in the afflicted regions, cetirizine and dexamethasone were employed.

CONCLUSION

Erythema multiforme has two major causes one being the immune-mediated viral infection and the second being the offending drug. Ruling out the exact cause lies in the precise assessment of ADR. Hence adopting a more precise method like scoring in the Naranjo scale

must be considered. In this case report, we intend to highlight the association between the offending drug i.e., phenobarbitone and erythema multiforme.

REFERENCES

1. Tripathi K. Essentials of Medical Pharmacology. Jaypee Brothers, Medical Publishers Pvt. Limited, 2008.
2. Erythema multiforme: Pictures, causes, treatment, and more [Internet]. Medical News Today. MediLexicon International; [cited 2022Jun2]. Available from: <https://www.medicalnewstoday.com/articles/323801>
3. R. Zankat DD, J. Sheth DH, G. Chaudhary DR, D. Malhotra DS, R. Patel DP. A case report on Phenobarbitone induced Stevens-Johnson Syndrome: An alarming hypersensitivity reaction. International Journal of Medical Research and Review, 2018; 6(3): 200–3.
4. Massot A, Gimenez-Arnau A. Cutaneous adverse drug reaction type erythema multiforme major induced by Eslicarbazepine. Journal of Pharmacology and Pharmacotherapeutics, 2014; 5(4): 271–4.
5. Gonzalez FJ, Carvajal MJ, del Pozo V, Lahoz C, Santamaria L, Blanca M, et al. Erythema multiforme to phenobarbital: Involvement of eosinophils and T cells expressing the skin homing receptor Journal of Allergy and Clinical Immunology, 1997; 100(1): 135–7.