

Phenytoin/albendazole induced exanthematous eruptions: a case report**M. Ravishankar*, N. Rakshith**

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ABSTRACT

Exanthematous drug eruptions, often called “drug rashes” or “maculopapular eruptions” by non-dermatologists are the most common form of cutaneous drug eruption. Cutaneous reactions are among the most common adverse effects of drugs, including penicillins, cephalosporins, sulfonamides, and allopurinol (with an incidence of up to 50 cases per 1000 new users), and particularly the aromatic amine anti-seizure medications, including carbamazepine, phenytoin, and lamotrigine (with an incidence of up to 100 cases per 1000 new users). Phenytoin is a hydantoin derivative anticonvulsant drug used primarily in the management of complex partial seizures and generalized tonic-clonic seizures. Albendazole is a benzimidazole medication used for the treatment of a variety of parasitic worm infestations. Carbamazepine and phenytoin are among the most common causes of antiepileptic drug-related cutaneous adverse reactions. Manifestations range from a mild erythematous maculopapular rash to life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis. Albendazole induced rashes and urticaria have been reported in less than 1% of the patients. Here we present the case of a 12-year-old male patient who came to the dermatology outpatient department with complaints of itching and maculopapular eruptions all over the body. The patient gave a history of taking tablet phenytoin and tablet albendazole for neurocysticercosis since 1-week. There was no fever or any other systemic manifestations. There was no history of any other drug intake. A diagnosis of phenytoin/albendazole induced exanthematous eruptions was made. Both the medications were discontinued, and the patient was advised to take syrup sodium valproate 200 mg BD. For the rashes and itching, the patient was advised to take tablet hydroxyzine HCl 10 mg OD, tablet prednisolone and tablet levocetirizine for 5 days. Improvement was seen and the itching reduced. Rechallenge was not done. In this event, casualty assessment using Naranjo adverse drug reaction probability scale revealed that phenytoin/albendazole were probable causes for the adverse drug reaction.

Keywords: Exanthematous eruptions, Drug rashes, Maculopapular eruptions, Morbilliform eruptions, Cutaneous drug eruptions, Adverse effects, Phenytoin, Albendazole, Cutaneous adverse reactions, Neurocysticercosis, Anticonvulsant, Anthelmintic, Delayed hypersensitivity reaction, T-cell mediated, Idiosyncratic, Macule, Papule, Erythematous, Immunological, Casualty assessment, Naranjo adverse drug reaction probability scale, Probable, Adverse drug reaction

INTRODUCTION

Exanthematous drug eruptions, often called “drug rashes” or “maculopapular eruptions” by non-dermatologists are the most common form of cutaneous drug eruption.¹ Cutaneous reactions are among the most common adverse effects of drugs, including penicillins, cephalosporins, sulfonamides and allopurinol (with an incidence of up to 50 cases per 1000 new users), and particularly the aromatic amine anti-seizure medications, including carbamazepine, phenytoin,

and lamotrigine (with an incidence of up to 100 cases per 1000 new users).²

A study by Chatterjee et al. shows that urticaria and fixed drug rashes were the most common morphological reaction-types. The most common offending drugs were carbamazepine (16.23%), phenytoin (15.15%) and cotrimoxazole (13.53%); however, antimicrobials were the most common drug group implicated.³ Various studies shows that most common morphologic patterns are

exanthematous, urticarial and/or angioedema, fixed drug eruption and erythema multiforme. Others have also noted exanthematous eruption to be the most common type of drug eruption. Exanthematous drug eruptions, also known as maculopapular drug eruptions, are the most common cutaneous skin reactions and represent approximately 95% of all cutaneous drug eruptions.

Phenytoin is a hydantoin derivative anticonvulsant drug used primarily in the management of complex partial seizures and generalized tonic-clonic seizures. Phenytoin is also used to prevent seizures following neurosurgery. Phenytoin is believed to protect against seizures by causing voltage-dependent block of voltage-gated sodium channels.⁴

Albendazole is a benzimidazole medication used for the treatment of a variety of parasitic worm infestations. It is a broad-spectrum anthelmintic, effective against roundworms, tapeworms, and flukes. Albendazole is used for a wide range of diseases caused by parasitic worms including: giardiasis, trichuriasis, filariasis, neurocysticercosis (NCC), hydatid disease, enterobiasis, and ascariasis among others.⁵

Carbamazepine and phenytoin are among the most common causes of antiepileptic drug-related cutaneous adverse reactions (Arif et al., 2007).⁶ Manifestations range from a mild erythematous maculopapular rash to life-threatening Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Albendazole induced rashes and urticaria have been reported in less than 1% of the patients.⁷

Here we discuss the case of a 12-year-old boy who developed an exanthematous rash after consuming phenytoin and albendazole for the treatment of NCC.

CASE REPORT

A 12-year-old male patient reported to the dermatology outpatient department (OPD), Adichunchanagiri Institute of Health Sciences and Research Centre (AH and RC) with complaints of maculopapular rash all over the body since 2 days. The patient gave a history of taking tablet phenytoin 50 mg OD and tablet albendazole 100 mg BD since 1-week. These medications were prescribed for the confirmed diagnosis of NCC by the radiology department, AH and RC with the help of a computerized tomography scan, a week ago. The patient had reported to the pediatrics OPD, AH and RC with a history of convulsions. On taking medications prescribed by the pediatrician for NCC, patient's condition improved and was discharged. After 2 days, patient gives h/o itching all over the body which initially started over both the upper arms and gradually spread all over the body. Maculopapular rashes developed subsequently, prompting the patient to seek medical advice. There was no other drug intake history. General physical examination and systemic examinations were

normal. The case was diagnosed as an allergic reaction induced due to the intake of phenytoin/albendazole. Both the medications were discontinued, and the patient was advised to take syrup sodium valproate 200 mg BD. For the rashes and itching, the patient was advised to take tablet hydroxyzine HCl 10 mg OD, tablet prednisolone and tablet levocetirizine for 5 days. Improvement was seen and the itching reduced. Rechallenge was not done (Figure 1a and b).

DISCUSSION

Anticonvulsant, antiparasitic, and anti-inflammatory agents (steroids) are used in the treatment of NCC. Phenytoin, carbamazepine, phenobarbital, and sodium valproate are the anticonvulsants used. Albendazole and praziquantel are the two main cysticidal drugs used for the treatment of NCC. Corticosteroids like prednisolone and dexamethasone are used for their anti-inflammatory action.

Exanthematous drug eruptions (also called morbilliform or maculopapular drug eruptions) are the most common drug-induced eruptions. They are a type of idiosyncratic, T-cell mediated, delayed (Type IV) hypersensitivity reactions. Exanthematous eruptions present as a widespread, symmetrically distributed rash composed of pink-to-red macules and papules that may coalesce to form plaques. Although mucous membranes are usually spared, redness without blistering may occur at these sites. Pruritus is frequent but highly variable in severity, and low-grade fever (temperature less than 38.5°C) is common.²

Review of morphological terms:

Macule: a flat skin lesion <1 cm in greatest diameter. When macules exceed 1 cm, the appropriate term is patch.⁸

Papule: a raised bump <1 cm in diameter. When papules exceed 1 cm in size, the appropriate term is plaque (palpable)



Figure 1: (a and b) Phenytoin-induced exanthematous eruptions.

lesions elevated above the skin surface) or nodule (a larger, firm papule with a significant vertical dimension).⁸

Exanthematous drug eruptions usually begin 4-21 days after the responsible drug is started and rapidly evolve into a widespread rash. Most drug-induced exanthematous eruptions evolve rapidly, are symmetric and widespread, reach the maximal extent within 2 days after the elimination of the causative drug, and fade within a week after the drug is eliminated. Some drug eruptions start to fade even while the patient is still taking the causative agent. The character of the individual lesions frequently varies according to the body site (e.g. confluent red plaques on the back and discrete pink macules and papules on the extremities). The rash is likely to be a deeper red and may even become purpuric in dependent areas. With the exception of patients who bleed easily, one should be able to cause blanching of the rash in non-dependent areas. First-time exanthematous drug eruptions typically begin to appear 4 to 21 days after the start of treatment.²

Lesions are typically erythematous or reddened, due to the presence of inflammation.

Commonly, the eruption in a given patient is a combination of macules, papules, patches, plaques, and even other morphologies, though on morphology may predominate.

Age may be the single most important predictive factor of diagnosis. In the absence of other data, maculopapular rash in adults is most likely to be drug related, while maculopapular rash in children is most likely to be viral related.

The duration of the eruption may be acute (recent onset, <4 weeks), sub-acute (4-8 weeks), or chronic (>8 weeks). These time frames are arbitrary.

An acute eruption often has a specific trigger, such as an allergic (e.g. medicine) or infectious (e.g. viral) exposure. The distribution of the eruption can be localized or generalized. Other clinical factors, including the presence of fever, headache, and other sign of illness, are of great importance. Some conditions with a serious clinical course have a maculopapular eruption as a presenting sign and evaluation should be carried out urgently.⁸

The primary differential diagnoses to consider for a maculopapular rash are:

Drug eruptions, viral exanthems, rickettsial infections, bacterial infection (including those that are toxin-mediated), systemic diseases (e.g. acute graft-versus-host disease and Kawasaki disease), and rheumatological diseases.⁸

Generally, a maculopapular eruption in the absence of fever or systemic manifestations is not urgent. When fever or illness is present, urgent illness must be considered. Several conditions with serious clinical course may

have a maculopapular eruption as a component, and evaluation should be carried out urgently if suspected. Among them are: meningococemia, anaphylactic reactions, TEN and SJS, drug reaction with eosinophilia and systemic symptoms, staphylococcal scalded skin syndrome and toxic shock syndrome, Rickettsial spotted fever.⁸

The underlying mechanism is likely to be immunological through cell-mediated hypersensitivity. Once a drug - or a hapten- is presented by Langerhans' cells to the T-lymphocytes, it can then bind covalently or noncovalently to MHC II-peptide complexes, which in turn activate both CD4 and CD8 positive T-cells, leading to a cytotoxic effect.⁹

Of note, however, is that sulfamethoxazole can bind directly to the MHC-peptide covalently.¹⁰

Treatment is supportive, initially the responsible drug is discontinued, and this is followed by the use of topical emollients and a moderate potency topical steroid. For significant pruritus, however, it is prudent to avoid systemic steroids that may cloud the picture if there is any diagnostic doubt or underlying infection. Sedative antihistamines may be used to relieve symptoms of pruritus.

In this event, casualty assessment using Naranjo adverse drug reaction probability scale revealed that Phenytoin/Albendazole were probable causes for the adverse drug reaction.¹¹

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