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Exanthematous allergic drug reactions due to four chemically unrelated drugs

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Among the various types of allergic skin eruptions associated with drugs, exanthematous reactions are most frequent [1, 2, 3]. Occasionally patients have exanthematous reactions to two different medications [2]. Cross sensitivity between chemically related drugs are also well known [2, 4]. Although exanthematous eruptions are well described in association with rifampicin [5], ethambutol [2, 6], phenobarbital [2], and phenytoin sodium [2, 3], there are no reports of one patient reacting to all of these.

Clinical synopsis

A 21-year-old woman without prior history of medication reactions developed itching and macular erythema all over her body 1 hour after taking phenytoin sodium 200 mg intravenously after a seizure. The eruption resolved within 2 days with dexamethasone 4 mg twice daily. Phenytoin sodium was replaced with phenobarbital 120 mg daily. Dexamethasone was continued. CT scan and MRI showed a space occupying lesions in the right frontal region suggestive of a tuberculous granuloma with edema. Sodium valproate (400 mg twice daily), mannitol, rifampicin (600 mg), isonicotinic acid hydrazide (INH) (300 mg), and pyrazinamide (1.5 g daily) were added. Phenobarbital (60 mg) and dexamethasone (8 mg daily) were continued. Mannitol was stopped after 7 days. Repeat MRI of brain after 7 days was still suggestive of inflammatory granuloma, most likely tuberculoma with abscess formation. Treatment was modified to phenobarbital (120 mg at night), ofloxacin (400 mg), rifampicin (600 mg), ethambutol (800 mg), INH (300 mg) and pyrazinamide (1.5 g daily), along with dexamethasone (8 mg daily). After 10 days, acetaminophen (500 mg), betahistine dihydrochloride (8 mg) and clobazam (20 mg) were added for use when needed. All the medicines were continued over the next 10 days without any problems. However, when dexamethasone was tapered and stopped during the next 12 days, she developed itching and macular erythema on her neck that spread all over the body during the next 4-5 days. Betamethasone 8 mg orally daily was added and betahistine dihydrochloride and paracetamol were stopped. However the eruption increased during the next 2 days without the development of mucosal lesions, lymphadenopathy, or fever. At this juncture all the drugs were stopped. Phenobarbital was replaced by clobazam 10 mg twice daily. During the next 24 hours the eruption began to subside and complete clearing occurred within 5 days; betamethasone was tapered and stopped over the next 3 days.

After 15 days, provocation tests were attempted after taking informed written consent from the patient. All the drugs taken by the patient were thus tested by giving orally as detailed in Table 1. Initially $\frac{1}{13}$ to $\frac{1}{2}$ of a 1-day therapeutic dose was given under supervision. If there was no reaction within 24 hours, the dose was increased to $\frac{2}{3}$ to 1-day therapeutic dose. If there was no reaction in the form of itching and erythema during the next 48 hours it was inferred that patient was not allergic to the drug. Each drug was tested in this way. Reactions were controlled with oral corticosteroids. Further provocation with remaining drugs was resumed only after complete clearance. There were no reactions with ofloxacin, clobazam, INH, pyrazinamide, acetaminophen, or sodium valproate.

However, she developed itching all over the body without erythema 8 hours after rifampicin 300 mg was given. The pruritus cleared on its own during next 3-4 hours. After challenge with her rifampicin 600 mg, within 2 hours she developed itching and macular erythema all over her body without any fever or constitutional symptoms. The reaction was controlled within 24 hours with betamethasone 6 mg given orally.

There was no reaction with 200 mg ethambutol given, but she developed itching (lasting 2 hours) without erythema, 12 hours after a 400 mg dose. After an 800 mg ethambutol dose, she developed itching and macular erythema all over her body that was controlled within 36 hours with 6 mg betamethasone given orally twice daily.

Phenobarbitol (30 mg) produced itching on the trunk and mild erythema after 3 hours; this improved on its own during next 12 hours. Phenobarbitol (60 mg) produced itching and erythema all over the body after 1 hour. The reaction was completely controlled within 2 days with betamethasone 4 mg orally twice daily.

Finally, she developed itching and erythema all over her body 20 minutes after 100 mg phenytoin sodium, controlled promptly with betamethasone 4 mg given orally.

Well after clearing, rechallenge tests were repeated sequentially with rifampicin (600 mg), phenobarbitol (60 mg), ethambutol (800 mg), and phenytoin sodium (100 mg). She developed itching and erythema all over her body with all the four drugs separately after 4.0, 1.5, 9.0 and 0.5 hours, respectively. Each time the reaction was controlled within 12-36 hours with 4-6 mg of betamethasone orally.

A biopsy taken from erythematous lesions on the back, after provocation with ethambutol, showed tiny spongiotic vesicles in the epidermis with a few lymphocytes in the vesicles. The dermis showed a moderate perivascular lymphocytic infiltrate consistent with, but not diagnostic of, drug eruption. There were no eosinophils seen in the dermal infiltrate. There were no abnormalities detected in liver and kidney function tests done after each reaction.

Discussion

The occurrence of itching and macular erythema all over the body within ½-12 hours on both the occasions following rechallenge/provocation with rifampicin, ethambutol, phenytoin sodium, and phenobarbitol given separately at intervals of 8-65 days, confirms the causal association of the erythematous macular eruption to all of the four drugs separately. Histopathology from an erythematous area was suggestive but not diagnostic for drug reaction.

Provocation tests are still considered to be the most reliable test for confirming the cause of allergic drug reactions [6, 7, 8, 9]. However many dermatologists hesitate to resort to provocation tests for fear of fatal consequences. After mild medication reactions, rechallenge may be attempted safely if done under supervision. It is incorrect to presume that a drug most commonly known to produce a drug reaction is responsible in every case. Sometimes, a drug not previously known to produce a reaction is found to be the causative one [10, 11, 12].

Antiepileptic drug hypersensitivity syndrome (ADS) manifests with rash, fever, and internal organ involvement [4]. It is presumed that this is because of a relative excess of reactive oxidative metabolites of aromatic antiepileptic drugs and insufficient detoxification. This results in cell death or contributes to the formation of antigen that triggers the immune reaction. Cross reactivity among the aromatic antiepileptic drugs, phenytoin, phenobarbitol, carbamazepine, and primidone are very common, as high as 70-80 percent. Two of our patients' drug reactions fall into this category (phenytoin and phenobarbitol).

A group of drug allergy patients show a marked tendency to react to several chemically unrelated drugs including antibiotics and anticonvulsants. This is called multiple drug allergic syndrome (MDAS) [14]. It is characterized by skin rash, fever, lymphadenopathy, and internal organ involvement. Multiple drug allergic syndrome is thought to be the result of the presence of tertiary and quaternary mono-, di-, and tri-alkyl amino-groups, especially methyl or ethyl groups. Thus, this syndrome seems to occur with a wide range of drugs containing tertiary amino and quaternary amino groups that are present in many different pharmacologically active agents. Another possible mechanism is that a non-specific patient-related factor leads to direct histamine release from the mast cells and basophils [15].

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) [16] or the drug hypersensitivity syndrome is a serious condition and manifests as a severe skin reaction with significant internal involvement (adenopathy, hepatitis, nephritis, interstitial pneumopathy, and eosinophilia). The main cause of death in this condition is severe visceral involvement. Common drugs incriminated include aromatic anticonvulsants, sulfonamides, and minocycline.

There was no lymphadenopathy, fever, or internal organ involvement in the present case and the skin reactions began promptly (within ½-12 hours). Her reactions do not fit well into the categories of multiple drug allergy syndrome (MDAS), drug induced hypersensitivity syndrome (DIHS), antiepileptic drug hypersensitivity syndrome (AHS), or DRESS Syndrome.

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