

Acute generalized exanthematous pustulosis due to diltiazem: Investigation of cross-reactivity with other calcium channel blockers



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Clinical Implications

- Calcium channel blockers are a group of widely used drugs, and allergic reactions due to diltiazem are frequently described. However, cross-reactivity among different calcium channel blockers is not well-studied. Our patient with acute generalized exanthematous pustulosis due to diltiazem had positive patch test results to diltiazem and verapamil but a negative patch test result to nifedipine.

TO THE EDITOR:

Acute generalized exanthematous pustulosis (AGEP) is a rare, but potentially serious, T-cell-mediated condition caused by drugs in 90% of cases. It is characterized by the sudden onset of erythematous edematous lesions with nonfollicular scattered micropustules, which typically start on the face and large folds. It is rarely associated with oral or mucosal erosions, systemic involvement, or fever. Cases of AGEP associated with calcium channel blockers (CCBs) have been reported, most frequently with diltiazem.¹ There are 3 groups of CCBs: benzothiazepines (diltiazem), phenylalkylamines (verapamil), and dihydropyridines (amlodipine, nifedipine, nimodipine, felodipine, nifedipine, and others). T-cell-mediated immunologic cross-reactivity among the 3 groups of CCBs has not been documented, and the chemical structures of the 3 groups are very different. This is the first case report of patch testing an individual with CCB-associated AGEP with all 3 groups of CCBs that could be identified on literature review.

We report a case of a 79-year-old woman with hypertension, treated for 3 months with amlodipine. She was then switched to diltiazem by her primary care physician because of poor blood pressure control. She developed a micropapular rash on the thorax and face after taking the diltiazem for 6 days. The rash then spread to the rest of the trunk, folds, and thighs, eventually affecting about 30% of her total body surface area. The rash evolved to confluent surface pustules. She had crusted erosions in labial and gingival mucosa and labial edema. She also developed fever. She was initially seen in the emergency department. Blood tests showed leukocytosis (16,800 μ L, 84% neutrophils and no eosinophilia); elevated acute-phase reactants (fibrinogen 588 mg/dL [normal 150-450 mg/dL] and C-reactive protein 2.8 mg/dL [normal 0-0.5 mg/dL];

creatinine 1.12 mg/dL [normal 0.5-0.90 mg/dL]); and elevated liver enzymes (ALT 60 U/L [normal 5-31 U/L], AST 45 U/L [normal 10-31 U/L], GGT 50 U/L [normal 6-40 U/L], and CK 257 U/L [normal 26-192 U/L]). The episode resolved in 10 days after the patient stopped diltiazem and treatment with methylprednisolone for 10 days. A skin biopsy was done at admission; the pathology described subcorneal spongiform pustules and spongiosis in the epidermis. There were perivascular infiltrates, interstitial inflammation, and polymorphonuclear eosinophils noted in the underlying dermis. The EuroSCAR score for AGEP² was 10 (definitive). Patch testing (PT) was performed (4 weeks after resolution of AGEP), using Curatest Nonwoven Epicutaneous Patch Test Strips (Lohman & Rauscher International, Rangsdorf, Germany) with diltiazem (in 10% petrolatum), verapamil (in 30% petrolatum), and nifedipine (in 2% petrolatum). Readings were done at 48 hours (D2) and 96 hours (D4). The patient had positive results on D2 and D4 with diltiazem and verapamil (induration and erythema of 4 and 5 mm, respectively) and negative test results with nifedipine (Figure 1). To document tolerance with nifedipine, an oral challenge test was proposed, but the patient refused any further testing.

AGEP is a rare entity, usually with a benign course, but can present with systemic symptoms. It is commonly (90%) drug-associated.¹ The typical clinical course begins abruptly, often within 24 to 48 hours after the introduction of the culprit drug, with fever ($>38.0^{\circ}\text{C}$) and a rash with sterile micropustules of 2 to 4 mm that affects the face and folds but quickly spreads to the rest of the body. Rarely, as in our case, it may be accompanied by mucosal lesions, and in some cases hepatic and renal impairment.¹ Treatment is based on withdrawal of the culprit drug, use of systemic steroids, and symptomatic treatment with antihistamines and emollients.¹ There have been several cases reported in the literature of AGEP associated with CCB use, particularly diltiazem,^{3,4} but none of them with nifedipine.

Gonzalo Garijo et al⁵ described 3 cases of other cutaneous reactions due to diltiazem, showing positive PT with this drug in all 3 of them. The study of cross-reactivity with other CCBs was studied in 2 of these patients. One case demonstrated a positive PT to nifedipine and tolerance of verapamil; the other case manifested a positive PT to verapamil and tolerance of nifedipine.

Other cases of cutaneous reaction to diltiazem reported in literature performed PT only with diltiazem (the culprit drug), with positive results, but not with other CCBs.⁶⁻⁹ It is noteworthy that cross-reactivity between CCBs appears to be variable based on the available data.¹⁰ In our patient, we observed cross-reactivity between diltiazem and verapamil, suggesting an unknown epitope from each drug with similar immunogenic characteristics.

In summary, we present a case of diltiazem-associated AGEP documented by positive PT, confirming type IV hypersensitivity.⁶ Cross-reactivity was noted between diltiazem and verapamil in our case. Although patch tests suggested lack of cross-reactivity with nifedipine, tolerance to nifedipine could not be confirmed by an oral challenge in our patient. We conclude that PTs are useful in cases of AGEP because they can confirm a type IV

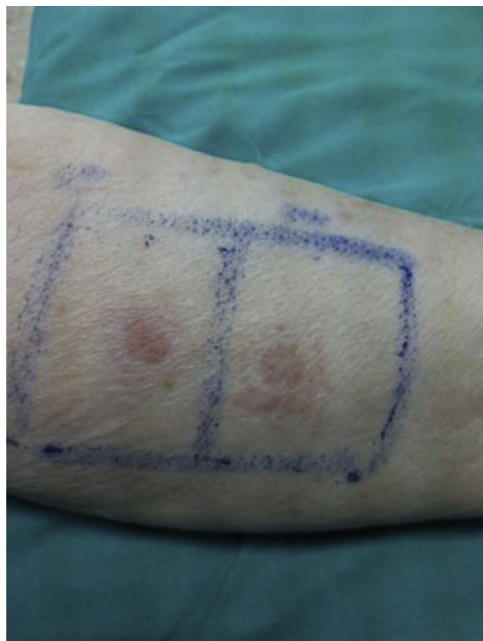


FIGURE 1. Positive skin PT with diltiazem and verapamil at D4.

hypersensitivity mechanism due to the drugs, and potentially help identify clinically significant cross-reactivity or lack of it among drugs in a therapeutic class.

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REFERENCES

1. Szatwoski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Acad Dermatol* 2015;7:843-8.
2. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. *J Cutan Pathol* 2001;28:113-9.
3. Fernández-Ruiz M, López-Medrano F, García-Ruiz F, Rodríguez-Peralto JL. Pustulosis exantemática aguda generalizada inducida por diltiazem: presentación de un caso y revisión de la literatura. *Actas Dermosifiliogr* 2009;100:719-40.
4. Messeguer F, Agustí-Mejías A, Requena C, Pérez Ferriols A. Claves diagnósticas de la pustulosis exantemática aguda generalizada. *Piel* 2011;26:7-11.
5. Gonzalo Garijo MA, Pérez Calderón R, de Argila Fernández-Durán D, Rangel Mayoral JF. Cutaneous reactions due to diltiazem and cross reactivity with other calcium channel blockers. *Allergol Immunopathol (Madr)* 2005;33:238-40.
6. Floristán Muruzábal MU, Feltes Ochoa RA, Feito Rodríguez M, Arranz DM, Casado Jiménez M. Fiebre y pústulas en paciente con pancreatitis aguda grave. *Rev Clin Esp* 2009;209:95-6.
7. Girardi M, Duncan KO, Tigelaar RE, Imaeda S, Watsky KL, McNiff JM. Cross-comparison of patch test and lymphocyte proliferation responses in patients with a history of acute generalized exanthematous pustulosis. *Am J Dermatopathol* 2005;27:343-6.
8. Gensch K, Hodzic-Avdagic N, Megahed M, Ruzicka T, Kuhn A. Acute generalized exanthematous pustulosis with confirmed type IV allergy: report of 3 cases [in German]. *Hautarzt* 2007;58:250-2. 254-5.
9. Serrão V, Caldas Lopes L, Campos Lopes JM, Lobo L, Ferreira A. Acute generalized exanthematous pustulosis associated with diltiazem [in Portuguese]. *Acta Med Port* 2008;21:99-102.
10. Cholez C, Trechot P, Schmutz JL, Faure G, Bene MC, Barbaud A. Maculopapular rash induced by diltiazem: allergological investigations in four patients and cross reactions between calcium channel blockers. *Allergy* 2003;58:1207-9.

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