

Cutaneous reactions due to diltiazem and cross reactivity with other calcium channel blockers

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ABSTRACT

Background: The spectrum of cutaneous eruptions in association with calcium channel blockers is extensive, varying from exanthemas to severe adverse events. Reactions due to diltiazem occur more frequently than with other calcium channel blockers. Patch testing has been used as confirmatory testing in patients with extensive cutaneous reactions. Cross-reactivity among these drugs have not been established.

Material: We present 3 patients: 1) A 54-year-old man developed a generalized erythema-multiforme-like reaction followed by erythrodermia and exfoliative dermatitis 6-7 days after starting on diltiazem. The drug was stopped and remission was obtained with emollients and systemic corticosteroids and antihistamines within 12 days. 2) A 80-year-old woman experienced a pruritic exanthematous eruption on her trunk which evolved to generalized erythrodermia and superficial desquamation. This reaction appeared 10 days after taking diltiazem, and gradually improved in 10-12 days after discontinuation of this drug. 3) A 79-year-old man presented with erythema and pruritus initially on the back, and then affecting thorax, extremities and face. He had started treat-

ment with diltiazem three days before. Diltiazem was stopped and steroid and antihistamine therapy was given. His skin condition improved, but 3 days later the patient received verapamil with worsening of previous situation. He recovered within 7 days.

Methods and results: Two to six months after the reaction, we carried out epicutaneous tests with calcium channel blockers from different groups. Diltiazem proved positive (at 48 and 96 hours) in the three patients; nifedipine was also positive in patient 2, and verapamil in patient 3. Controlled administration of verapamil was well tolerated in patient 2 after the reaction, and the patient 1 has taken nifedipine without problems.

Conclusions: 1) We report 3 cases of cutaneous reactions due to diltiazem. 2) Epicutaneous tests have been useful for diagnosis. 3) As one of patients had positive patch tests to diltiazem and nifedipine, and other one with diltiazem and verapamil, more studies are needed to demonstrate cross reactions among calcium channel blockers.

Key words: Calcium channel blockers. Cross reactions. Delayed hypersensitivity. Diltiazem. Patch tests.

RESUMEN

Introducción: El espectro de las reacciones cutáneas producidas por los antagonistas del calcio es extenso, abarcando desde exantemas hasta reacciones graves. El diltiazem es el implicado con más frecuencia. Para el diagnóstico, las pruebas epicutáneas son útiles en las reacciones cutáneas extensas. La reactividad cruzada entre estos fármacos no ha sido establecida.

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Material: se presentan tres pacientes: 1) Varón de 54 años, que desarrolló una reacción eritema multiforme-like que evolucionó a eritrodermia y dermatitis exfoliativa, 6-7 días después de iniciar tratamiento con diltiazem. Mejoró en 12 días tras suspender el fármaco y recibir tratamiento con emolientes y corticoides y antihistamínicos sistémicos. 2) Mujer de 80 años que sufrió una erupción exantemática en el tronco, con evolución a eritrodermia y descamación superficial, 10 días después de comenzar a tomar diltiazem. Mejoró a los 10-12 días de interrumpirlo. 3) Varón de 79 años que presentó al 3er. día de tratamiento con diltiazem eritema y prurito, al principio en la espalda y luego en tronco, extremidades y cara. Mejoró al suspenderlo, pero volvió a empeorar al tomar verapamilo.

Métodos y resultados: Se realizaron pruebas epicutáneas con diltiazem y otros antagonistas del calcio 2-6 meses después de la reacción. Diltiazem fue positivo en los 3 pacientes (a las 48 y 96 h); nifedipino fue también positivo en el paciente 2 y verapamilo en el paciente 3. Verapamilo fue administrado de forma controlada al paciente 2 con buena tolerancia y el paciente 1 ha tomado nifedipino sin problemas.

Conclusiones: 1) Comunicamos 3 casos de reacciones cutáneas producidas por diltiazem. 2) Las pruebas epicutáneas han sido útiles para el diagnóstico. 3) En uno de los pacientes las pruebas epicutáneas fueron positivas para diltiazem y nifedipino y en otro paciente la positividad fue al diltiazem y verapamilo, por lo que son necesarios más estudios para demostrar la reactividad cruzada entre los antagonistas del calcio.

Palabras clave: Calcio-antagonistas. Diltiazem. Hipersensibilidad. Patch tests. Reacciones cruzadas.

INTRODUCTION

The spectrum of cutaneous eruptions in association with calcium channel blockers is extensive, varying from exanthemas to severe adverse events (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome reaction, acute generalized exanthematous pustulosis...) ¹⁻¹². Reactions due to diltiazem occur more frequently than with other calcium channel blockers ¹⁻⁴. The mechanism of these reactions is unknown, and it is likely that the pathophysiology differs with each reaction. Patch testing has been used as confirmatory testing in patients with extensive cu-

taneous reactions ^{2,4,5,7-11}. Cross-reactivity among these drugs have not been established.

CASE REPORTS

Case 1

A 54-year-old man developed a generalized erythema-multiforme-like reaction followed by erythrodermia and exfoliative dermatitis 6-7 days after starting on diltiazem. He had increased white blood cell count with eosinophilia. A skin biopsy showed intraepidermal vesicular dermatitis, ballooning degeneration of keratinocytes and mixed-cell infiltrate. The drug was stopped and remission was obtained with emollients and systemic corticosteroids and antihistamines within 12 days.

Case 2

A 80-year-old woman experienced a pruritic exanthematous eruption on her trunk which evolved to generalized erythrodermia and superficial desquamation. This reaction appeared 10 days after taking diltiazem, and gradually improved in 10-12 days after discontinuation of this drug. We have no information about the treatment administered to the patient.

Case 3

A 79-year-old man began treatment with diltiazem for managing hypertension. Three days later, he presented with erythema and pruritus initially on the back, and then affecting thorax, extremities and face. Diltiazem was stopped and steroid and antihistamine therapy was given. His skin condition improved, but 3 days later the patient received verapamil with worsening of previous situation. He recovered within 7 days.

Two to six months after the reactions, we carried out epicutaneous tests with calcium channel blockers from different groups: benzothiazepines (diltiazem), phenylalkylamines (verapamil), and dihydropyridines (nifedipine, nimodipine, nicardipine, nitrendipine, amlodipine, lacidipine and lercanidipine). Diltiazem proved positive (at 48 and 96 hours) in the three patients; nifedipine was also positive in patient 2, and verapamil in patient 3 (table I). The same tests were negative in 10 control patients. Controlled administration of verapamil was well tolerated in patient 2 after the reaction, and the patient 1 has taken nifedipine without problems.

Table I
Epicutaneous tests with calcium channel blockers

Drug	Concentration Vehicle	Patient 1		Patient 2		Patient 3	
		48 h	96 h	48 h	96 h	48 h	96 h
Diltiazem	6.25 mg/ml*	++	++	++	++		
	5-10 % pet			+	+		
	30 % pet					-	++
Verapamil	2.5 mg/ml*	-	-	-	-	-	+
	30 % pet					-	+
Amlodipine	5-10 % pet			-	-		
	30 % pet					-	-
Felodipine	30 % pet					-	-
Lacidipine	5-10 % pet			-	-		
	30 % pet					-	-
Lercanidipine	5-10 % pet			-	-		
	30 % pet					-	-
Nicardipine	5-10 % pet			-	-		
Nifedipine	10 mg/ml*	-	-	++	++	-	-
Nimodipine	0.2 mg/ml*	-	-	-	-	-	-
	30 % pet					-	-
Nitrendipine	5-10 % pet			-	-		

*commercialized forms as is; pet: petrolatum.

DISCUSSION

Maculopapular exanthema is the most common cutaneous adverse reaction to diltiazem. We describe 3 patients with different cutaneous reactions due to this drug (eythema-multiforme-like reaction, erythrodermia and a pruritic exanthematous eruption).

According to the literature, patch tests with diltiazem are useful in diagnosing cutaneous adverse reactions with this drug. Positive results have been reported using commercialized forms of diltiazem as is^{5,6} or diluted at 10 mg/ml⁸, 1 % pet^{7,10,11}, 5-10 % in pet or water⁹ or 30 % in water, petrolatum or alcohol⁴. In case of severe reactions, these tests should be performed with caution and beginning with low concentrations^{4,13}.

There are no consensus about cross reactions among calcium channel blockers. The review of the literature shows few papers referred to this subject and different results^{2,4-6,10,11}. It is difficult to come to conclusions as the clinical presentation of patients and methodology used for the diagnosis are different. Some authors suggest cross reactions between diltiazem and nifedipine¹², amlodipine⁶ or verapamil⁴ (by patch tests^{2,4} or regarding clinical reactions^{6,12}), but no others^{5,10,11}. In our case, all the patients had positive patch tests with diltiazem. In addition to that, the patient 2 had positive patch tests with nifedipine (but tolerated verapamil), and the patient 3 with verapamil (in

fact, he worsened when he took this drug). It is difficult to establish the meaning of this results as we have not performed controlled administration of these drugs.

Regarding our results and others previously reported, in case of adverse cutaneous reactions to diltiazem, we suggest to perform patch tests with this drug and other calcium channel blockers (the concentrations should be established taking into account the severity of the reaction)¹³. Once confirmed the positivity of diltiazem, it would be possible to administer some of the calcium channel blockers with negative patch test result under hospital surveillance.

Conclusions: 1) We report 3 cases of cutaneous reactions due to diltiazem. 2) Epicutaneous tests have been useful for diagnosis. 3) Although one of our patients had positive patch tests to diltiazem and nifedipine and the other one with diltiazem and verapamil, more studies are needed to establish cross reactions among calcium channel blockers.

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