

CONTACT POINT

Contact dermatitis caused by diltiazem cream and cross-reactivity with other calcium channel blockers

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Contact sensitization to calcium channel blockers (CCBs) is a rare phenomenon. However, the increased use of various topical preparations containing diltiazem may result in more reports of contact allergies. We present a patient who developed severe contact dermatitis after using a diltiazem cream for treatment of an anal fissure.

Three classes of CCB are used in clinical practice: benzothiazepine type (eg, diltiazem), dihydropyridine type (eg, nifedipine), and phenylalkylamine type (eg, verapamil) (Figure S1). However, all CCBs selectively inhibit L-type calcium channels, resulting in reduced movement of calcium ions into muscle cells. Interestingly, patch testing in our patient showed not only a positive skin reaction to diltiazem itself, but also cross-reactivity with 2 other chemically non-related CCBs, namely, nifedipine and verapamil.

CASE REPORT

A 47-year-old healthy man, without a history of atopic disease, experienced a generalized papular rash starting from the anogenital area. Nine days earlier, he had commenced topical treatment of an anal fissure. The emollient in question was a pharmacy preparation including 2% lidocaine and 2% diltiazem hydrochloride individually formulated in basic skin cream (Bepanthen Wund- und Heilsalbe; Bayer Vital, Leverkusen, Germany). After a few days, the patient developed an eczematous eruption in the anogenital area, and this was followed by rapid dissemination of the skin lesions to the trunk and extremities. The rash improved with topical glucocorticoid treatment and cessation of the diltiazem cream. Two weeks later, the patient restarted treatment of the anal fissure with the same cream, and the rash reappeared. A second identical pharmacy preparation of the cream without diltiazem was applied on several occasions, without any problems. The past medical history was negative for arterial hypertension and systemic intake of any CCB.

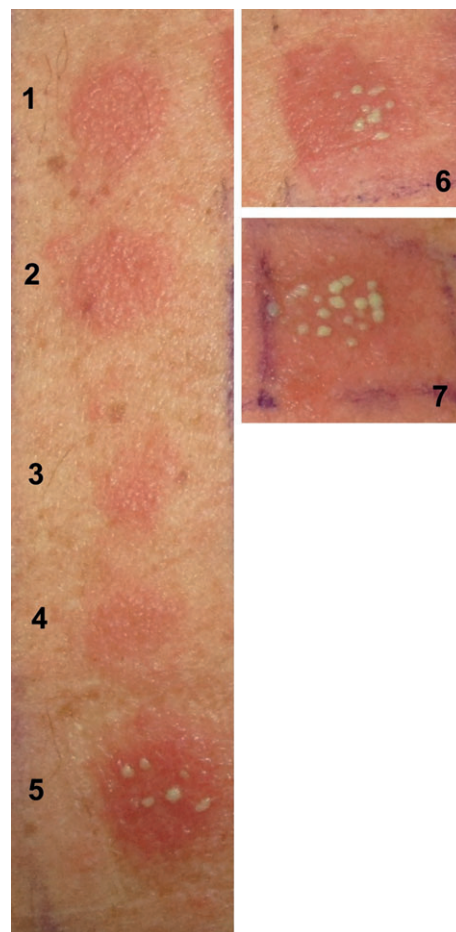


FIGURE 1 Results of patch testing on day 3: 1, nifedipine 1% pet.; 2, nifedipine 10% pet.; 3, verapamil hydrochloride 1% pet.; 4, verapamil hydrochloride 10% pet.; 5, diltiazem hydrochloride 1% pet.; 6, diltiazem hydrochloride 10% pet.; 7, anal cream (containing 2% diltiazem hydrochloride)

TABLE 1 Patch test reactions to the anal cream containing 2% diltiazem, and the pure compounds diltiazem hydrochloride, nifedipine and verapamil hydrochloride in 1% and 10% pet. each

Drug	Concentration and vehicle	Day 1	Day 2	Day 3	Exposure time (days)
Anal cream (with 2% diltiazem hydrochloride and 2% lidocaine)		+++	+++	+++	1
Diltiazem hydrochloride	1% pet.	++	+++	+++	1
Diltiazem hydrochloride	10% pet.	++	+++	+++	1
Nifedipine	1% pet.	–	?+	++	2
Nifedipine	10% pet.	–	?+	++	2
Verapamil hydrochloride	1% pet.	–	–	+	2
Verapamil hydrochloride	10% pet.	–	–	+	2

The patient was referred for further diagnostic procedures. Patch testing with the baseline series of the German Contact Dermatitis Research Group and additional series of local anaesthetics (including lidocaine hydrochloride 15% pet.) and topical pharmaceutical substances, including dexpanthenol 5% pet., showed no relevant positive reactions. The patch test with the patient's cream containing 2% diltiazem hydrochloride "as is" showed a positive skin reaction: at day [D] 2, +++; D3, +++; D7, ++. Additional patch testing with diltiazem hydrochloride 1% and 10% pet. was performed with 1 day exposure (CAS no. 3328622-5; 10% test preparation purchased from Chemo-technique, Vellinge, Sweden; moreover, a 1:10 dilution in pet. was tested). Two other CCBs from different chemical groups (nifedipine and verapamil) were selected and patch tested using 2 day exposure (1% and 10% in pet. each; preparation in-house; chemicals from Sigma Aldrich, Taufkirchen, Germany). We found strong positive reactions to diltiazem and nifedipine, and positive reactions to verapamil (Figure 1; Table 1). One healthy individual, tested as a control, did not show any reactions to patch tests with all of these test preparations containing CCBs. As the patient never took CCBs orally, we suggested oral provocation test with nifedipine and/or verapamil for assessment of the relevance of the positive patch test reactions. However, the patient refused any provocation procedures. Thus, we recommended avoidance of all CCBs, owing to the positive patch test reactions.

DISCUSSION

Our patient experienced 2 allergic contact dermatitis events after topical use of an individually prepared anal fissure cream containing 2% diltiazem hydrochloride. The culprit was easily identified, because the patient had repeatedly used an identical cream without diltiazem without symptoms. Patch testing demonstrated contact sensitization to diltiazem. The patient also had positive skin reactions to nifedipine and verapamil. To the best of our knowledge, diltiazem is the only CCB that is available as commercialized topical preparation in selected European countries. Although contact allergy to topical diltiazem has been reported earlier,^{1–5} nobody has addressed cross-reactivity with other CCBs so far.

There are more publications reporting cutaneous side-effects after oral intake of diltiazem than cutaneous side-effects after topical application.^{6–8} However, exclusively anecdotal observations have been published on cross-reactivity of the pharmacologically different

CCBs after oral intake. Some authors reported recurrent cutaneous reactions after oral administration even of different classes of CCB,^{7,9,10} whereas a switch to a different CCB was well tolerated in another patient.⁷

With regard to skin testing in 3 patients with rashes caused by oral diltiazem, patch tests showed positive reactions to diltiazem (5% to 30% pet. and/or 6.25 mg/mL of the readily available commercial injection solution) and nifedipine (10 mg/mL of the commercial injection solution) in 1 patient. The second individual showed positive reactions to diltiazem and verapamil (30% pet.), whereas the third patient showed no cross-reactivity.⁷ Two other case reports have described cross-reactivity in patch testing between diltiazem (10% or 30% pet.) and verapamil (30% pet.), but not with nifedipine (2% to 30% pet.).^{6,8} It is of note that the concentrations of CCBs in the patch test preparations diverged significantly, and ranged from 2% to 30% pet.^{6,7} Our patient showed cross-reactivity to nifedipine (1% and 10% pet.) and, to a lesser extent, to verapamil (1% and 10% pet.). There is no consensus in the current literature on how CCBs should be patch tested. In most published cases of allergy testing after oral intake of CCBs, the authors failed to precisely describe all aspects of the patch test procedures (commercially available drug or chemical, vehicle, test concentration, and exclusion of irritative test preparations in healthy individuals).

In contrast to our report and other reports of cross-reactivity of CCBs, the chemical structures of the 3 different classes do not show similarities that may easily explain these findings. As none of the aforementioned reports on contact dermatitis caused by CCBs addressed cross-reactivity, no patient was evaluated for oral tolerance to different CCBs. As no data exist on the sensitivity and specificity of the various patch test conditions for CCBs, we recommend evaluating the relevance of these findings by oral provocation tests after rigorous risk-benefit considerations until more data become available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Fig. S1. Chemical structures of (a) diltiazem, (b) nifedipine, (c) verapamil.

