

Systemic acyclovir reaction subsequent to acyclovir contact allergy: which systemic antiviral drug should then be used?

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Allergic contact dermatitis caused by acyclovir is rare. We report the 5th case of systemic acyclovir reaction subsequent to acyclovir contact dermatitis, with investigations made to determine an alternative antiviral treatment. A 23-year-old woman, after dermatitis while using Zovirax[®] cream, went on to develop urticaria after oral acyclovir. Patch tests were performed with the components of Zovirax[®] cream (acyclovir, propylene glycol and sodium lauryl sulfate) and with other antiviral drugs. Patch tests were positive to Zovirax[®] cream, acyclovir, valacyclovir and propylene glycol. Patch and prick tests with famciclovir were negative, but its oral administration caused an itchy erythematous dermatitis on the trunk and extremities. Our patient developed a systemic acyclovir reaction subsequent to acyclovir allergic contact dermatitis, with cross-reactions to valacyclovir and famciclovir. Their common chemical structure is the 2-aminopurine nucleus. It is probably this part of the molecule that provokes both contact allergy and systemic reactions. The only antiviral drugs not having this core are foscarnet and cidofovir, and these could therefore be alternatives.

Keywords: acyclovir; allergic contact dermatitis; antiviral drugs; cross-reactions; cutaneous adverse drug reactions; medicaments; oral provocation test; patch tests; systemic. © Blackwell Munksgaard, 2003.

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Allergic contact dermatitis caused by acyclovir is rare but can occur. In patients with such dermatitis from this antiviral drug, oral acyclovir can elicit a systemic cutaneous adverse drug reaction. From our case and a review of the literature, we tried to determine what other antiviral drugs, such as valacyclovir or famciclovir, could be used in such patients.

Patient and Methods

A 23-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip and right cheek. She had previously applied Mupiderm[®] (mupirocin) (Pharmaform, Paris, France), Hexomedine[®] (hexamidine) (Theraplix, Montrouge, France) and a cream containing acyclovir 5% and propylene glycol (Zovirax[®] cream) (Glaxo Wellcome, Marly le-roi, France) for recurrent herpes simplex of the lips. The dermatitis rapidly healed after stopping these creams and antiseptics and with Diprosept[®] (betamethasone and clioquinol) application. The

patient had no previous history of atopy or allergic contact dermatitis.

A few months after the resolution of the dermatitis, 6 hr after beginning oral acyclovir (Zovirax[®]), the patient developed an urticaria with itchy, erythematous, oedematous lesions on the trunk and extremities. Acyclovir was stopped while the patient received oral antihistamines (Clarityne[®], loratadine) (Schering-Plough, Levallois-Perret, France) and the urticaria disappeared in 24 hr.

15 months after the disappearance of the urticaria, patch tests were performed with the European standard series, an excipients and preservatives series (Chemotechnique, Malmö, Sweden), Mupiderm[®] (mupirocin), Hexomedine[®] (hexamidine), Zovirax[®] cream, Zovirax[®] ophthalmic ointment, Zovirax[®] tablet, sodium lauryl sulfate 0.1% aq., hexamidine 0.1% aq. and propylene glycol 5% in petrolatum (pet.). To study potential cross-reactions, patch tests were also applied with Oravir[®] tablet (famciclovir, hydroxypropyl cellulose, sodium carboxymethylcellulose and magnesium stearate) (Smith Kline Beecham, Nanterre, France) and Zelitrex[®] tablet (valacyclovir, cellu-

lose, crospovidone, povidone, K 90, magnesium stearate and silica) (Glaxo Wellcome) diluted at 30% pet., alc. and aq., according to the guidelines for drug skin tests of the European Society of Contact Dermatitis (1).

Prick tests were also performed with a crushed Oravir[®] tablet. Oral administrations of famciclovir with progressively increased dosages (0.05 mg; 1 hr later, 0.5 mg; 1 hr later, 5 mg; 3 hr later, 50 mg; and 2 hr later, 500 mg) were also performed.

Results

The skin-test results are summarized in Table 1. There were positive patch tests to Zovirax[®] cream, Zovirax[®] tablet and Zovirax[®] ophthalmic ointment, in which the only common component was acyclovir, thus confirming sensitization to acyclovir. The patient also had positive patch tests to propylene glycol and valacyclovir.

As patch tests and prick tests with famciclovir were negative, oral administration of famciclovir, with progressively increased dosages, was carried out. Unfortunately, an itchy erythematous dermatitis occurred on the trunk 15 hr after administration of the last dose of famciclovir of 500 mg. The dermatitis rapidly subsided after oral loratadine treatment was started. There was no relapse of any dermatosis after 4 months of follow-up.

Discussion

Contact allergy to acyclovir might appear to be rare, as only 20 cases have been reported in the literature (2), but it is probably underdiagnosed. Usually, contact allergy to acyclovir appears a few days after the beginning of the topical treatment, but in some cases, it appears several years after recurrent use of topical acyclovir.

Patch tests with acyclovir can be negative (3) in sensitized patients. Sometimes, patch tests are

positive to Zovirax[®] cream but not to any of its various components tested separately. This could be because of 'compound allergy' (4) or due to the difficulty in obtaining sufficient penetration of acyclovir through the epidermis without the use of propylene glycol. Sensitization to Zovirax[®] cream can be due to the excipients' sodium lauryl sulfate and, especially, propylene glycol (5, 6), and more rarely due to acyclovir (7–9).

20 cases of systemic reactions secondary to oral administration of acyclovir in patients in whom previous use of topical acyclovir was not known have been collected by Carrasco et al. (10). There were varied clinical features, including vesicular dermatitis, dermatitis of the palms and soles, peripheral oedema, erythema nodosum, exanthems, hyperhidrosis, acne, lichenoid eruption, pruritus, rash, urticaria, vasculitis and alopecia. Systemic acyclovir reactions subsequent to acyclovir allergic contact dermatitis have very rarely been reported.

A 19-year-old woman (11) had a lip dermatitis after application of Zovirax[®] cream. Patch tests with acyclovir (1, 3 and 5% pet.) and propylene glycol 10% aq. were positive. She developed an urticaria 15 min after administration of 2 intravenous infusions of acyclovir (250 mg). 2 cases of concomitant sensitization to 2 components of Zovirax[®] cream, acyclovir and propylene glycol, were reported by Bayrou et al. (12). The same 2 patients had systemic dermatitis (maculopapular rash or eczema) after oral acyclovir. An oral provocation test with famciclovir (250 mg, 4× in 1 day) gave no reaction in 1 case but elicited a systemic reaction in the 2nd case.

Lammintausta et al. (13) reported the case of a woman taking oral valacyclovir. After taking the 1st tablet, she developed an exanthem on the face, trunk and extremities. Patch tests with acyclovir and cetearyl alcohol were positive. Oral administration of famciclovir elicited a systemic reaction. Valacyclovir is the L-valine ester of acyclovir and is almost completely metabolized to acyclovir after oral administration. Therefore, valacyclovir seems clearly not to be indicated in cases of acyclovir allergy. Famciclovir may also not be an alternative choice, because 3 of 4 oral administrations (3 previously reported cases and the case herein reported) in patients with contact allergy to acyclovir elicited a systemic reaction.

Cross-reactions between acyclovir, valacyclovir and famciclovir could be due to their close chemical structures. The chemical structure common to acyclovir, famciclovir and valacyclovir is the 2-aminopurine nucleus. This is probably the part of the molecule that activates the immunologic mechanism responsible for provoking both contact allergy and systemic reactions.

Table 1. Patch tests and prick tests results

Test substances	Patch tests		Prick tests
	D2	D4	
Nickel sulfate 5% pet.	+	+	
Trolamine	+	+	
Mupiderm [®] cream	–	–	
Hexamidine 0.1% aq.	–	–	
Zovirax [®] cream 50% pet.	++	++	
Zovirax [®] ophthalmic ointment as is	++	++	
Zovirax [®] tablet	+	+	
Sodium lauryl sulfate 1% aq.	–	–	
Propylene glycol 5% pet.	–	+	
Oravir [®] 50% pet.	–	–	–
Zelitrex [®] 30% pet., aq., alc.	+	+	

alc., alcohol; aq., water; Pet., petrolatum.

This core is also found in ganciclovir but not in foscarnet or cidofovir. Therefore, we propose that these latter 2 drugs could be alternatives in the case of severe herpetic infection in patients with negative patch tests with these 2 molecules. But, to our knowledge, no case has yet been reported to confirm this hypothesis.

In conclusion, patch tests seem useful in the case of contact and systemic allergy to drugs containing acyclovir, to determine whether acyclovir and excipients are responsible for inducing the adverse drug reaction. In the case of sensitization to acyclovir, it seems advisable to propose testing with other antiviral drugs. From our results and those from literature, cross-reactions with valacyclovir and famciclovir seem to be frequent. According to our analysis of the chemical structures of antiviral drugs, foscarnet or cidofovir could be the alternative drug, although further studies are necessary to confirm this hypothesis.

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