

# No evidence of contact sensitization to acyclovir in acute dermatitis of the lips following local application of Zovirax cream

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We report 4 patients with acute contact dermatitis of the lips following application of Zovirax cream. Patch tests with pure acyclovir, and combinations of the ingredients of the cream base, with and without acyclovir, provided no evidence of sensitization to any constituent of the cream.

*Key words:* acyclovir; irritant contact dermatitis; medicaments. © Munksgaard, 1995.

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Contact allergy to acyclovir has previously been reported in 4 patients (1-4), and, recently, 4 cases of contact sensitization to Zovirax cream with negative patch tests to its ingredients were published (5-8). Here, we report 4 other patients with acute dermatitis of the lips after topical use of Zovirax cream.

## Case Reports

During 1992 and 1993, 4 patients attended our outpatient department with severe oedematous vesicular eruptions of the lips and surrounding skin, which had appeared 1 to 3 days after applying Zovirax cream for herpes simplex infection. Patient no. 2 had first noticed improvement of her lesions, but, after applying the cream for 3 days, the lesions had worsened again. In 1 case (patient no. 3), the cream had previously been regularly used without any problem. In the case of each of the 4 patients, the clinical diagnosis was herpes simplex labialis with secondary acute contact dermatitis from Zovirax cream.

Patch tests were performed, at the earliest, 3 weeks after the lesions had healed. A special acyclovir series (Table 1), the German standard series, drug, ointment and preservative series were applied for 1 day to the patient's upper back. Readings were performed after 1, 2 and 3 days. Pure acyclovir (5 and 10% pet.), Zovirax ophthalmic ointment and the cream base without acyclovir were additionally applied for 2 days, and tested after removing the horny layer of the skin by the skin stripping method (9). Weak positive reactions

were obtained with Zovirax cream alone (patient no. 1) or with both Zovirax cream and the acyclovir-free cream base provided directly from the company (patient nos. 2-4).

Sodium acyclovir (therapeutically used in solution for intravenous therapy) gave irritant reactions in 2 patients. The pH of the solutions prepared in our pharmacy (5 and 10% aq.) was between 10 and 11.

Patch tests with pure acyclovir (5 and 10% pet.), obtained in larger amount (5 g) from the manufacturer, were negative in all 4 patients, even after applying the patches for 2 days or after skin stripping with adhesive tape. No reaction was recorded to Zovirax ophthalmic ointment (as is). This ointment was then used therapeutically on patient nos. 2 and 3 without any problem.

In an attempt to explain these discrepant results, and with regard to the possibility of compound allergy (5), further patch tests were performed. Pure acyclovir and poloxamer 407 procured from the company were combined with cetostearyl alcohol and propylene glycol in petrolatum. Still no reaction was recorded (Table 1).

Control tests in 10 healthy volunteers with Zovirax cream, sodium acyclovir and the acyclovir-free cream base also gave weak positive results in 8 patients (Table 2).

## Discussion

Acyclovir is a widely used antiviral drug that inhibits the DNA polymerase of human herpes virus-

Table 1. Patch test results

Patients		Case no. 1			Case no. 2			Case no. 3			Case no. 4			
		F, 22			F, 13			F, 41			M, 39			
Sex, age (years)		D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D4
<i>Series A</i>														
1.	Zovirax cream (as is)	+	+	+	-	+	-	-	+	=	+	+	-	-
2.	Zovirax ophthalmic ointment (as is)	-	-	-	-	-	-	-	-	-	-	-	-	-
3.	cream base (as is)	-	-	-	-	-	-	-	+	-	-	-	-	-
4.	acyclovir (A) 5% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
5.	acyclovir 10% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
6.	sodium acyclovir 5% aq.	-	-	-	-	-	-	-	IR	-	-	-	-	-
7.	sodium acyclovir 10% aq.	-	-	-	-	-	IR	-	IR	-	-	-	-	-
8.	cetostearyl alcohol (C) 20% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
9.	propylene glycol 40% MHEC	-	-	-	-	-	-	-	-	-	-	IR	-	-
10-12.	propylene glycol (P) 5%, 10%, 20% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
13-14.	propylene glycol 10%, 20% aq.	-	-	-	-	-	-	-	-	-	-	-	-	-
15-16.	poloxamer 1%, 10% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
17.	poloxamer (Po) 1% aq.	-	-	-	-	-	-	-	-	-	-	-	-	-
18.	Na lauryl sulfate 1% aq.	-	-	-	-	IR	IR	IR	IR	-	-	-	-	-
19.	paraffin (as is)	-	-	-	-	-	-	-	-	-	-	-	-	-
20.	petrolatum (as is)	-	-	-	-	-	-	-	-	-	-	-	-	-
21.	butylated hydroxyanisole 2% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
22.	butylated hydroxytoluene 2% pet.	-	-	-	-	-	-	-	-	-	-	-	-	-
<i>Series B</i>														
1.	A (5%)+C (6, 75%)+ P (20%)+Po (1%) in pet.		NT		-	-	-	-	-	-	-	-	-	-
2.	A+Po+P		NT		-	-	-	-	-	-	-	-	-	-
3.	A+Po+C		NT		-	-	-	-	-	-	-	-	-	-
4.	A+P +C		NT		-	-	-	-	-	-	-	-	-	-
5.	C+Po+P		NT		-	-	-	-	-	-	-	-	-	-
6.	A+Po		NT		-	-	-	-	-	-	-	-	-	-
7.	A+C		NT		-	-	-	-	-	-	-	-	-	-
8.	A+P		NT		-	-	-	-	-	-	-	-	-	-
9.	C+P		NT		-	-	-	-	-	-	-	-	-	-
10.	C+Po		NT		-	-	-	-	-	-	-	-	-	-
11.	P+Po		NT		-	-	-	-	-	-	-	-	-	-
<i>Stripping test</i>														
1.	Zovirax ophthalmic ointment (as is)		NT		-	-	-	-	-	-	-	-	-	-
2.	cream base (as is)		NT		-	+	-	-	+	-	-	-	+	+
3-4.	acyclovir 5%, 10% pet.		NT		-	-	-	-	-	-	-	-	-	-
<i>2-day application</i>														
1.	Zovirax ophthalmic ointment (as is)		NT		-	-	-	-	-	-	-	-	-	-
2.	cream base (as is)		NT		+	-	-	+	-	-	-	+	+	
3-4.	acyclovir 5%, 10% pet.		NT		-	-	-	-	-	-	-	-	-	

+ : erythematous, slightly infiltrated patch test area

- : negative patch test. IR: irritant reaction. NT: not tested.

es. Experimental sensitization of guinea pigs revealed low sensitizing power of acyclovir when compared with tromantadine (10). This may explain why cases of contact allergy to Zovirax cream are rare, despite its widespread use.

The 4 patients reported here had positive patch tests to Zovirax cream, but not to its ingredients or to Zovirax ophthalmic ointment. Patch testing with different constituents of the cream or combinations of these constituents did not help to identify an allergen. Given the fact that identical weak positive reactions were obtained in 8 control patients at 2 or 3 days, allergic contact sensitization seems unlikely.

These results are more compatible with some irritant property of the cream used. The cream base contains 40% propylene glycol, which may also induce irritation of the skin. Application of Zovirax

Table 2. Control patch tests in 10 healthy volunteers

		+D2	+D3	total
Zovirax cream	as is	4	1	5/10
cream base	as is		1	1/10
sodium acyclovir	5% aq.			0/10
sodium acyclovir	10% aq.	2		2/10

cream on acute herpetic lesions may thus, in some cases, result in worsening of the symptoms.

As indicated by the manufacturer, and in the literature (11, 12), acyclovir is soluble in water to a maximum concentration of 1.3 mg/ml. If larger quantities of the pure substance are used, this results in a solution separating out in just a few minutes (own experiment). Patch tests using this solution produce a deposit of powder on the skin after 1 day. This also applies to sodium acyclovir 10% aq.

As stated by some authors (8), non-response to acyclovir in patients with positive patch tests to Zovirax cream might also be the result of its failure to penetrate through the epidermis.

In our 4 patients, we consider that Zovirax cream caused acute dermatitis of the lips, or was at least responsible for worsening of the lesions. Despite patch testing with the different constituents of the cream in various concentrations and combinations, and using the skin stripping method, only irritant or weak positive reactions were obtained. This does not exclude compound allergy, or even true allergic contact sensitization in some patients, but it seems to indicate that irritant contact dermatitis should also be considered.

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