

Drug skin tests in cutaneous adverse drug reactions to pristinamycin: 29 cases with a study of cross-reactions between synergistins

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The present study was made to determine the value of drug skin tests in patients with cutaneous adverse drug reactions (CADRs) due to a synergistin (pristinamycin) and to determine the frequency of cross-reactions between synergistins. 29 patients were referred during the onset of the CADR due to pristinamycin: 18 with maculopapular rash, 9 erythrodermas, 1 angioedema and 1 Stevens–Johnson syndrome. They all had patch tests with pristinamycin and, in most cases, with other synergistins [virginiamycin and dalfopristin–quinupristin (DQ)], prick tests (10 cases) and intradermal tests (IDT) (5 cases). Skin tests with synergistins were positive in 27 cases, patch tests with pristinamycin in 20/29 cases (69%), prick tests with pristinamycin in 3/9 cases on immediate (1 case) or on delayed (2 cases) readings, and IDT with DQ in 4/5 cases. Cross-reactions between synergistins occurred in 9/22 with virginiamycin and in 7/8 cases with DQ. Skin tests with synergistins are useful in investigating CADR due to pristinamycin. Synergistins are composed of 2 chains (1 depsipeptide and 1 macrocyclic lactone) with many structural analogies between all synergistins. According to the chemical structures and our results, it seems advisable to avoid all synergistins in patients with CADR due to pristinamycin.

Key words: cutaneous adverse drug reaction; dalfopristin–quinupristin; drug intradermal tests; drug patch tests; drug prick tests; pristinamycin; synergistin antibiotics; virginiamycin. © Blackwell Munksgaard, 2004.

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Drug skin tests have been reported to be helpful in diagnosing cutaneous adverse drug reactions (CADRs) due to pristinamycin, but this has been reported in only a small number of patients.

Pristinamycin is a drug belonging to the class of synergistin antibiotics also called streptogramin antibiotics. 3 streptogramins are, or have been, commercialized: pristinamycin (Pyostacine[®], Aventis Laboratory, Paris, France), virginiamycin (no longer commercialized) and dalfopristin–quinupristin (DQ) (Synercid[®], Aventis Laboratory). Pyostacine[®] is commercialized for oral intake (pristinamycin, wheat starch, silica, white dextrin, magnesium stearate, hypromellose, macrogol 6000 or 20000 and titanium dioxide). Staphylomycine[®] (virginiamycin) was commercialized for oral intake and topical application. It was a frequently used anti-infectious ointment in France. Recently, an injectable form of streptogramin has been commercialized under the trade name of Synercid[®] (DQ, methasulfonic acid, sodium hydroxide and

nitrate). Pristinamycin was extracted from *Streptomyces pristinaespiralis* in 1955 and virginiamycin from *Streptomyces virginiae* in 1954. Dalfopristin is a semisynthetic polyunsaturated macrolactone, and quinupristin is a semisynthetic depsipeptide. All the streptogramin antibiotics are composed of two chains, a depsipeptide and a macrocyclic lactone (Table 1). The depsipeptides are pristinamycin I_A in pristinamycin, virginiamycin S1 in virginiamycin and quinupristin is pristinamycin I_A plus a quinuclidinyl thiomethyl radical. The macrocyclic lactones are pristinamycin II_A both in pristinamycin and in virginiamycin and dalfopristin is pristinamycin II_A plus a diethylaminoethylsulfonyl radical. Therefore, chemical structures are close between all the streptogramin antibiotics.

This unicentre study was made to determine the value of drug skin tests in patients with a CADR due to pristinamycin and also to determine the frequency of cross-reactions between synergistin antibiotics.

Table 1. Main components in synergistins

	Depsipeptide	Macrocyclic lactone
Pristinamycin	Pristinamycin I _A	Pristinamycin II _A
Virginiamycin	Virginiamycin S ₁	Pristinamycin II _A = virginiamycin M1
Synercid [®]	Quinupristin = pristinamycin I _A + quinuclidinyl thiomethyl radical	Dalfopristin = pristinamycin II _A + diethylaminoethyl sulfonyl radical

Patients and Methods

Patients

A unicentre retrospective study was made, including all the patients who were referred to our Dermatology department from 1992 to 2002 and passing very strict inclusion criteria:

- (1) They all had well-defined clinical features as they were referred during the onset of the CADR.
- (2) The CADR was due to pristinamycin, with a high imputability (I₃ in 28 cases and I₄ in 1 case with angioedema), according to Moore et al. criteria (1), either because pristinamycin was the only recently introduced new drug or because the patient developed 2 onsets of CADR during 2 separate treatments with pristinamycin.
- (3) All patients had drug skin tests during the 6 months following the disappearance of the CADR.

29 patients (13 females, 16 males and mean age = 59 years, 16–93 years) were included. The clinical features of the CADR were maculopapular rash (MPR) in 18 cases, erythroderma in 9 cases, angioedema in 1 case and Stevens–Johnson syndrome in 1 case. The clinical features are summarized in Table 2. The patients reported that, in 1/2 cases, the CADR occurred during the 1st intake of pristinamycin, but it was impossible to confirm this and to be sure that none of these patients had previously used virginiamycin, for example during their infancy. None of these patients had previously received Synercid[®].

Methods

During the 6 months following the disappearance of the CADR, all patients had drug patch tests and other drug skin tests according to the guidelines published by the European Society of Contact Dermatitis (2). In all patients, patch tests were made with pristinamycin dispersed at 10% in petrolatum (pet.) and in water (aq.) and the commercialized pills containing pristinamycin diluted at 30% in pet and aq. In 4 cases, patch tests were also performed with pristinamycin diluted at 1% in pet. Patch tests were also performed with virginiamycin (contained in a

commercialized ointment) in 22 cases. In the more recent cases, patch tests were performed with Synercid[®] in powder dispersed at 30% in pet. Patch tests were put on the back under Finn Chambers[®] on Scanpor tape[®] (Epitest, Tuusula, Finland), read at 20 min, then on D2, D4 and 1 week later if negative.

When patch tests were negative, prick tests with pristinamycin and other synergistins (10 cases) were performed. They were performed on the forearm, read at 20 min and on D1, and their results were compared to those obtained with negative (0.9% saline) and positive (codeine phosphate at 9%) controls.

Then, when prick tests were negative on immediate readings, in the most recent cases, intradermal tests (IDTs) with Synercid[®] were performed (5 cases) on the external aspect of the arm by injecting 0.04 ml of sterile dilutions from 10⁻⁴ to the pure, commonly used dilution for treatment purposes. In the 3 most recent cases, dilutions were injected from 10⁻⁴ to 10⁻¹ dilutions, with immediate and delayed readings at 24 h.

Results

Skin tests with synergistin antibiotics were positive in 27/29 cases (Table 2).

Patch tests were positive with pristinamycin in 20/29 cases (69%). 12 controls, recruited as previously defined (2), had negative results on patch tests performed with pristinamycin dispersed at 10% in pet. In 1/4 cases, patch tests with pristinamycin were negative when tested at 1% in pet., but positive at 10% in pet.

Prick tests with pristinamycin were positive in 3/9 cases, on immediate reading in an angioedema and on delayed readings at D1 with synergistins in 2 cases (1 with only pristinamycin and 1 with both pristinamycin and Synercid[®]). In 1 patient with an MPR, 3 h after the carrying out of a prick test with pristinamycin, pruritus and a slight MPR appeared on the tested arm. 2 weeks later, the patient had another prick test with pristinamycin, and the same reaction occurred. In another patient, multiple patch tests were made with a commercialized form of pristinamycin diluted at 30% in pet. and pristinamycin diluted at 10% in

Table 2. Clinical features and results of drug skin tests in 29 cases of cutaneous adverse drug reactions due to pristinamycin

Patients	Sex	Age	Clinical features	Imputability	Patch test pristinamycin	Prick test pristinamycin	Patch test virginiamycin	Patch test Synercid®	Prick test Synercid®	IDT Synercid®	Reactivation
1	Female	65	MPR	I ₃	+	-					3 h after prick test (twice controlled)
2	Female	50	MPR	I ₃	+		+				
3	Female	45	MPR	I ₃	+		+				
4	Male	51	MPR	I ₃	+						
5	Female	73	MPR	I ₃	+		+				
6	Male	35	MPR	I ₃	+		+				
7	Female	61	MPR	I ₃	+		-				
8	Female	70	MPR	I ₃	+		-				
9	Male	63	MPR	I ₃	+						+ (MPR)
10	Male	63	MPR	I ₃	+		+				
11	Female	64	MPR	I ₃	+						
12	Male	32	MPR	I ₃	-		-				
13	Female	39	MPR	I ₃	+						
14	Female	65	MPR	I ₃	-	+ delayed	-	-	-	+ delayed	
15	Male	70	MPR	I ₃	-	+ delayed	-	-	+ delayed	+ delayed	
16	Male	55	MPR	I ₃	-	-	-	-	-	+ delayed	
17	Male	75	MPR	I ₃	-	-	-	-	-	-	
18	Female	60	MPR	I ₃	+		-				
19	Male	70	ED	I ₃	+		-				
20	Male	81	ED	I ₃	+		-				
21	Male	93	ED	I ₃	+		-				
22	Male	30	ED	I ₃	+		+				
23	Male	70	ED	I ₃	+		+				
24	Female	16	ED	I ₃	-		+				
25	Male	30	ED	I ₃	-		+				
26	Female	88	ED	I ₃	-					+ delayed	
27	Male	59	ED	I ₃	+		-	+	-		
28	Female	81	Urticaria	I ₄	-	+ immediate	-	-	+ immediate		
29	Male	53	SJS	I ₃	+		-	+			

CADR = cutaneous adverse drug reaction; ED = erythroderma; IDTs = intradermal tests; MPR = maculopapular rash; reactivation = reactivation of the CADR due to skin tests with pristinamycin; SJS = Stevens Johnson Syndrome.

pet., leading to a relapse of the MPR spreading over the whole back.

IDTs with Synercid[®] were positive in 4/5 cases on delayed readings (4 negative control patients).

Compared to the results obtained in 3 volunteers, all belonging to our medical staff, we determined that IDT performed with Synercid[®] seemed to be specific up to the 10^{-1} concentration in the injectable form, but the pure injectable form induced irritation and non-specific reactions.

This means that the upper concentration to use for IDT has to be quinupristin at 1.5 mg/ml and dalfopristin at 3.5 mg/ml.

Cross-reactions between synergistins were observed in 9/22 cases with virginiamycin and in 7/8 cases with Synercid[®].

Discussion

CADR due to pristinamycin are rare. This streptogramin can induce immediate or delayed reactions, as observed in this study. In our patients, most of the cases were MPRs or erythrodermas. None of them developed an acute generalized exanthematous pustulosis (AGEP). During the same period, we observed 2 cases of AGEP due to pristinamycin, but as the patients refused any further investigations, they were not included in this study. In most of the cases, delayed reactions due to pristinamycin occurred a few hours or 1–3 days after the intake of the antibiotic, with or without a previous history of synergistin intake. This short delay of onset after the beginning of the treatment has been previously reported (3). As already published, some patients could have been sensitized by previous topical use of virginiamycin (3), but this was impossible to be demonstrated in our patients.

In a previous article (4), the mechanism involved in MPR and erythrodermas due to pristinamycin was studied by immunophenotyping on biopsy samples taken during the CADR and on positive patch tests. We demonstrated that the mechanism involved was delayed cellular hypersensitivity mostly mediated by perivascular activated CD4⁺ cells expressing HLA DR but not CD25. Endothelial cells were activated with expression of CD62E [endothelial leukocyte adhesion molecule (ELAM)-1 and E-selectin] in 3/4 erythrodermas and 1/3 MPR due to pristinamycin. Satellite cell necrosis was sparse, but activation of keratinocytes was observed, expressing CD54 (ICAM 1) in 5/7 CADRs due to pristinamycin but HLA DR in only 2/7 cases. Unexpected labelling was observed with CD62L (L-selectin) throughout the epidermis in 4/7 cases and also on 1 positive drug patch test performed

on 1 of these 4 patients. CD62L is a selectin usually expressed by T cells.

As MPR or erythrodermas due to pristinamycin seem to be related to delayed cellular hypersensitivity, drug skin tests can reproduce this immunological mechanism and would be of value in investigating these CADRs due to pristinamycin.

With our study, which has the largest published number of patients suffering from CADRs due to pristinamycin, who have been tested with the suspected drug, we confirm the value of patch tests with pristinamycin in investigating CADR due to this synergistin, as was suggested by previous reports in smaller series 2/3 (3), 2/2 (5), 9/11 (6) and 8/9 (7). 69% of the 29 patients had positive patch tests to pristinamycin. As 1 patient had positive patch test with pristinamycin diluted at 10% in pet. but was negative when tested at 1% in pet., we suggest testing at 10% in pet. Our results also emphasize that, when skin tests with pristinamycin are negative, skin tests with other synergistin antibiotics can be positive, as in the cases where we observed positive results with virginiamycin (2 cases) and with Synercid[®] (2 cases).

To our knowledge, these are the 1st reported cases of delayed positive prick tests with pristinamycin and Synercid[®]. For the 1st time, we also report a relapse of a slight MPR following a prick test performed with pristinamycin, even without any reaction on the site of the test.

For the 1st time, we also report positive results in testing a recently commercialized streptogramin in injectable form (Synercid[®]). From our results, patch tests with Synercid[®] in powder form diluted at 30% in pet. and prick tests with the same drug at the usual concentrate seem to be specific. IDTs can be performed, but they seem to be specific only up to the 10^{-1} dilution from the usual concentration. We emphasize that prick tests and IDTs with streptogramin antibiotics have to be read both at 20 min and on D1. We did not observe any more delayed reactions in patients with negative prick tests or IDTs on D1 readings.

From our results, it seems possible to follow the guidelines summarized in Table 3 for investigating CADR due to pristinamycin. These guidelines seem of value as 27 of 29 tested patients had positive investigations. They also seem to be specific, as we did not observe false-positive results in 12 controls for patch tests and in 3 controls for IDT with Synercid[®]. But a larger number of controls would be necessary to determine the specificity of these drug skin tests.

Cross-reactions between synergistins were observed in 9/22 cases with virginiamycin and in 7/8 cases with Synercid[®]. Considering the numerous structural analogies between all synergistins,

Table 3. Guidelines for performing drug skin tests in patients suffering from cutaneous adverse drug reactions due to pristinamycin

Patch tests with pristinamycin (diluted at 10% in petrolatum) read at 20 min, day 2 and day 4 ↓
 If negative, prick tests (with dilutions of synergistins in cases of urticaria) ↓
 If negative, patch tests with other synergistin antibiotics ↓
 If negative, prick tests with other synergistin antibiotics ↓
 If negative, IDT to Synercid® until the 10⁻¹ concentration ↓

For both tests, immediate and delayed readings are required.
 IDT = intradermal tests.

according to the chemical structures and our results, it seems advisable to avoid all synergistins in patients with CADRs due to pristinamycin.

The responsible determinants involved in these immediate and delayed drug hypersensitivities are unknown. It is not possible to determine whether the cross-reactions are related to the analogies observed in the depsipeptide or in the macrocyclic lactone chains. As macrocyclic lactones (i.e. pristinamycin II_A) are identical in pristinamycin and virginiamycin, and as 8 patients had positive patch tests with pristinamycin without any cross-reaction with virginiamycin, we might suppose that in these patients, the sensitization to pristinamycin was due to the non-common chain, that is to say, the depsipeptide pristinamycin I_A.

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