Patch tests with popular topical antifungal drugs in eczema patients

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SUMMARY

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Study background: topical antifungal drugs are widely used, mostly without confirmation of fungal etiology of the treated skin disease. This may lead to increased risk of sensitisation. The aim of the study was to assess the frequency of positive patch test reactions to most popular antifungals in eczema patients, previously treated by general practitioners with topical imidazole antifungals. Study group: 68 eczema patients, 45 females and 23 males, aged 14-71 years, referred by general practitioners to the dermatology unit for diagnosis after a period of "empirical" therapy including topical antifungals.

Patch test were carried out with the 5 most popular topical antifungals in Poland: Clotrimazolum 1% cream (clotrimazole), Polfungicid 5% ointment (chlormidazole), Mycospor 1% cream (bifonazole), Pevaryl 1% cream (econazole), and Daktarin 2% cream (miconazole). The drugs were applied for 48 hours using IQ chambers. Positive patch tests reactions were found in 6 subjects (2 females and 4 males), who comprised 8.8% of the population studied. Four subjects were reactive to 2 different antifungals and 2 subjects reacted each to one drug. Mycospor 1% cream and Pevaryl 1% cream provoked positive reaction each in four subjects, Clotrimazolum 1% cream and Daktarin 2% cream elicited reactions each in one subject tested. No positive reaction was observed to Polfungicid 5% ointment. The author concludes that prolonged use of topical antifungal preparations is capable of inducing contact allergy either to the active substance or to the vehicle ingredients. Therefore, the philosophy of trying some "empirical" antifungal therapy without a mycological confirmation should be waived.

Key words: antifungal therapy side effects; topical antifungals; drug allergy; eczema patients; patch test

STRESZCZENIE

Testy płatkowe z popularnymi lekami przeciwgrzybiczymi u chorych na wyprysk

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Powszechne stosowanie miejscowych leków przeciwgrzybiczych, zazwyczaj bez mikologicznego potwierdzenia grzybicy, może powodować wzrost ryzyka uczulenia na te leki. Celem badania było określenie częstości występowania w testach płatkowych dodatnich odczynów na zewnętrzne leki przeciwgrzybicze wśród chorych na wyprysk, leczonych uprzednio przez lekarzy ogólnych. Badana grupa to 68 chorych na wyprysk, 45 kobiet i 23 mężczyzn w wieku od 14 do 71 lat, skierowanych na konsultację do poradni dermatologicznej po okresie terapii „empirycznej" lekami przeciwgrzybiczymi.

Pięć najbardziej popularnych w Polsce leków przeciwgrzybiczych: Clotrimazolum 1% krem (klotrimazol), Polfungicid 5% maść (chlormidazol), Mycospor 1% krem (bifonazol), Pevaryl 1% krem (ekonazol) i Daktarin 2% krem (mikonazol) aplikowano w 48-godzinnej okluzji z zastosowaniem komór IQ.

Dodatnie odczyny skórne stwierdzono u 6 osób (2 kobiet i 4 mężczyzn), które stanowiły 8,8% badanych. Cztery osoby zareagowały jednocześnie na 2 leki, a dwie na jeden lek. Kremy Mycospor 1% i Pevaryl 1% wywołały dodatnie odczyny, każdy u 4 osób, Clotrimazolum 1% i Daktarin 2% – każdy u jednej osoby. Nie stwierdzono reakcji na maść Polfungicid 5%.

Miejscowe leki przeciwgrzybicze mogą powodować uczulenie kontaktowe na substancję aktywną lub na składniki podłoża. Z tego powodu w przekonaniu autora filozofię „empirycznego" leczenia przeciwgrzybiczego bez mikologicznego potwierdzenia grzybicy należy odrzucić.

Słowa kluczowe: skutki niepożądane leczenia przeciwgrzybiczego; zewnętrzne leki przeciwgrzybicze; alergia na leki; chorzy na wyprysk; testy płatkowe

Antifungal drugs belong to the most widely used topical drugs, similar to topical corticosteroid preparations. Their wide use may lead to an increased risk of developing contact allergy, either to the active agent or to the vehicle. The aim of this study was to assess the frequency of skin reactions to topical antifungals among patients who had previously received antifungal therapy. The working question was

whether topical antifungal preparations are capable of causing contact skin sensitisation. Commercial preparations were selected because such preparations are used during therapy and the risk of developing contact allergy to any vehicle ingredient needs to be considered equally as seriously as to the active antifungal substance.

MATERIAL AND METHODS

68 patients were studied, 45 females and 23 males, aged 14-71 (median 40.5) years. All the patients were referred by general practitioners to the dermatology unit for diagnosis after a period of "empirical" therapy, which consisted mostly of topical antifungals and corticosteroids. The first criterion for including a patient into the study group was the presence of eczema which had been treated by a general practitioner for at least one year without success. The second criterion for inclusion was the necessity to carry out patch testing during the diagnostic evaluation. The third criterion was a positive answer to the question "have you ever received any anti-fungus topical preparation for your skin problems?" which was supplemented by listing trade names of antifungals available in Poland. All subjects who met all three criteria underwent patch testing with the 5 topical antifungals most popular in Poland which were added to European Standard series.

Five commercially available topical antifungals, purchased from a local pharmacy, were used for testing. These were Clotrimazolum 1% cream (producer: GlaxoWellcome, Poland; active ingredient: clotrimazole), Polfungicid 5% ointment (ZFA Unia, Poland; chlormidazole), Mycospor 1% cream (Bayer, Germany; bifonazole), Pevaryl 1% cream (Cilag, Belgium; econazole), and Daktarin 2% cream (ICN Polfa Rzeszów, Poland; miconazole). The drugs were applied on the clinically healthy skin on the back, using the inert additive free polyethylene plastic chambers on hypoallergenic non-woven adhesive tape (IQ chambers Chemotechnique Diagnostics AB, Sweden). The chambers were removed after 48 hours and the skin reaction was read immediately as well as 24 and 48 hours later. The skin reaction was recorded using the scoring recommended by the International Contact Dermatitis Research Group, where: "-" stands for negative reaction; "?" for doubtful reaction; "+" for weak, non-vesicular, reaction with erythema, infiltration and papules; "++" means strong, oedematous or vesicular, reaction; "+++" – extreme, ulcerative of bullous reaction; and "IR" – irritant reaction. Reactions with "soap-washed", glazed appearance or pustules were considered irritant [2].

RESULTS

Positive patch test reactions were found in 6 subject tested (2 females and 4 males), who constituted 8.8% of the population studied. 17.4% males and 4.4% females tested reacted to at least one antifungal. Detailed results are shown in table 1. A typical pattern of the reaction included erythema with some scarce tiny papules, recorded as "+" according to the International Contact Dermatitis Research Group scoring. No strong reactions were observed. Four subjects were reactive to two different antifungals and 2 subjects reacted to one of the tested drugs. Mycospor 1% cream and Pevaryl 1% cream provoked positive reaction each in 4 subjects, Clotrimazolum 1% cream and Daktarin 2% cream elicited reactions each in one tested subject. No positive reaction was observed to Polfungicid 5% ointment.

Table 1. Description of patients with positive patch tests

Patient	O.A.	P.K.	W.T.	P.E.	G.S.	G.M.
Sex	m	f	m	f	m	f
Age	27	38	30	44	55	37
Total number of positive reactions	2	2	2	2	1	1
Mycospor 1% cream	+	+	-	+	+	-
Pevaryl 1% cream	+	+	+	-	-	+
Daktarin 2% cream	-	-	+	-	-	-
Clotrimazolum 1% cream	-	-	-	+	-	-
Polfungicid 5% ointment	-	-	-	-	-	-

DISCUSSION

According to general opinion, contact allergies to imidazole antifungals are relatively rare, if their high prescription rates are taken into account [4, 12]. Only several dozen cases of contact reaction to all kinds of imidazoles were described. In 1991, a meta-analysis of 56 reported cases was completed: reactions to miconazole were the most common (23 of 56 cases), there were also 5 described subjects with contact allergy to clotrimazole, and 4 to econazole [1]. To the author's knowledge, there have been no reported cases of contact allergy to bifonazole and chlormidazole to date. *Hausen* et al. [6, 7] carried out an extensive study on the sensitising capacity of imidazole derivatives in guinea pigs. They concluded that miconazole, clotrimazole, econazole, and chlormidazole possess a low sensitising potency. They also made an interesting observation that although bifonazole had shown

a moderate sensitising potency in the animal model, no contact sensitisation to this drug in humans has been reported in the literature so far. *Gip* [5] showed that bifonazole in petrolatum, even in a concentration 32-fold higher than in the original product, had failed to provoke irritant reaction in eczema patients.

In this study, topical preparations were used as these are available to the patient from a pharmacy. There were several previous case reports where the eliciting allergens in antimycotic preparations proved not to be the imidazole itself. The most noteworthy are those reported by *Wade* et al. [14]. In this report, among 6 described subjects with allergic reaction to miconazole cream, 3 subjects demonstrated positive reaction in the occlusive patch test with vehicle; in contrast no positive reaction to 2% miconazole in petrolatum was found. In two other cases of contact dermatitis caused by the clotrimazole cream, the first one was caused by octyldodecanol [3] and the second by benzyl alcohol [11]. The above data suggest that an allergic reaction to vehicle ingredients of the drugs tested may be responsible for most reactions described in this paper. This is also supported by the fact that the Polfungicid ointment, in which the vehicle was petrolatum and not a cream base, did not elicit skin reaction in any of the subjects tested.

In this study, antifungals were applied under 48-hour occlusion which promotes the penetration of the drug into skin and may thus aggravate its allergising or irritating potency. Under normal circumstances the drugs are applied without occlusion, on the other hand however, these are applied on the diseased skin, which means that the epidermal barrier is damaged and more penetrable compared to the unchanged skin on which the patch testing was carried out. Moreover, in typical circumstances the drugs are used for long periods, typically weeks or even months.

Regarding the sex of the tested persons, 17.4% males and 4.4% females reacted to at least one antifungal. Males made up 66.6% of all patch test reactive persons while they comprised only 33.8% of all the subjects tested. A possible explanation may be that women in general are more concerned about their health and, therefore, consult a dermatologist sooner than men, thus avoiding a long term "empirical" therapy associated with a higher risk of developing allergy. However, the described excess in patch test reactive men did not prove statistically significant.

In a textbook for general practitioners [10], readers are encouraged to resign from an "academic diagnosis" of fungal infection in favour of an ill-defined term "picture of fungal infection" which does not imply a laboratory confirmation of the fungus presence. This kind of "making medicine" is dangerous for many reasons, not least because of increased expenses for a non evidence-based therapy. Prolonged use of topical drugs is connected with an increased risk of developing contact allergy to them [9], and patients with pre-existing eczema (such as the subjects of this study) are at an even higher risk of contact sensitisation [8]. Moreover, patients referred to a dermatologist after a period of "empirical" therapy (mostly with topical glucocorticosteroids and antifungals) have a lower chance for an accurate diagnosis because of the changes in the clinical picture [13]. This study seems to shed light on yet another risk connected with "empirical" therapy – an increased risk of becoming sensitised to drugs unnecessarily applied without proper clinical justification.

CONCLUSION

Topical antifungal preparations are capable of inducing contact allergy. Therefore, the philosophy of trying a "probatory" antifungal therapy without a mycological confirmation should be waived.

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