

tions of 5-FU. We believe this distinction in positive reactions is very important for the clinical and therapeutic consequence of the treatment of these patients and therefore suggest that patch testing should be performed with Efudix® cream and its ingredients when allergic contact dermatitis is suspected in patients undergoing this treatment.

Efudix® cream or topical 5% 5-FU is an antimitotic agent used to treat premalignant and malignant skin lesions (1). It usually elicits a moderate to severe irritant contact dermatitis with erythema and scaling at the site of the application, and symptoms of burning, pruritus and stinging. Although several cases have been reported in literature (1–8), allergic contact dermatitis from Efudix® cream seems to be uncommon, given its widespread use (2). To our knowledge, we are the first to report a series of 14 patients in whom an allergic contact dermatitis was suspected, and in whom the different ingredients of the cream were also patch tested.

Allergic contact dermatitis because of topical use of 5-fluorouracil (Efudix® cream)

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We suspected 14 patients treated for actinic keratoses at our outpatient clinic to have allergic contact dermatitis to Efudix® cream because of an extensive reaction to the cream or a prolonged healing process not usually associated with Efudix® cream. We tested these patients with (ingredients of) Efudix® cream and with serial dilutions of the active ingredient 5-fluorouracil (5-FU). We observed positive reactions to vehicle components and also to serial dilu-

Materials and Methods

Patients

Between 2004 and 2006, 14 patients (7 women and 7 men, aged 51–80 years) presenting with symptoms of a possible allergic contact dermatitis during topical use of 5-FU cream (Efudix® cream) because of actinic keratoses, were seen at our outpatient clinic. Symptoms consisted of erythema, severe itching, swelling and ulcerations at the site of application of Efudix® cream and skin beyond, more severe and extensive than the reaction expected from the topical use of Efudix® cream. No other involving factors (e.g. sun exposure) could explain the severity and extent of the reaction. The application sites involved were the face, the vertex, the lower legs and/or the dorsa of the hands. The duration of the initial treatment was 3–4 weeks with a frequency of 2 daily applications. The earliest reaction was observed in 1 patient 10 days after initial treatment with Efudix® cream. In the remaining patients, the extensive skin reactions developed during a second or a third treatment with Efudix® cream because of an unsatisfactory response to initial treatment.

Patch testing

All patients were investigated by closed patch tests using Finn Chambers® (8 mm) and Fixomull® tape, applied in a standardized order to their back with Efudix® cream (ICN Pharmaceuticals, Zoetermeer, the Netherlands) as is and diluted 0.1% and 1% pet., as well as with all the ingredients individually: propylene glycol (20% pet.), methyl- and propyl parahydroxybenzoate (both 3% pet.), stearyl alcohol (30% pet.), polysorbate 80 (5% pet.), sorbitan monooleate (5% pet.), and 5-FU in serial dilutions as described earlier in literature (0.1%, 1% and 5% in saline) (1,2). After an early reading 20 min after application, occlusion for 2 days followed. Reactions were additionally read on day 2 (D2), D4 and D7 and were scored and interpreted following the International Contact Dermatitis Research Group (ICDRG) protocol (9).

Results

Patch test results of the patients are shown in Table 1. 10 patients had one or more positive reactions. 4 patients had no positive reaction. 8 patients had positive reactions to one or more dilutions of 5-FU. 7 of these patients also had a positive reaction to Efudix® cream as is, and the remaining patient (patient 4) showed a weak reaction to Efudix® cream 1% pet., which could not be reproduced.

Figure 1a and b shows the reactions in patient 13 on D2 and D4, respectively. The higher the concentration of 5-FU, the more intense was the reaction on D4. When the results of the D2 and D4 readings were compared, the characteristic crescendo reaction of contact allergy was observed.

We asked all patients whether they were prepared to undergo the patch testing again to see if the results were reproducible. Only patients 4, 6 and 10 were willing to be retested. The earlier reactions in patient 4 could not be reproduced. The reactions of patient 6 were reproducible and the reactions at a later date were more severe than the initial reactions: Efudix® cream (0.1% pet.) 2+, Efudix® cream (1% pet.) 3+, Efudix® cream as is 3+, 5-FU (1% NaCl) 3+ and 5-FU (5% NaCl) 3+. In patient 10, the reaction to sorbitan monooleate (5% pet.) was reproducible at a later date, but the reaction to polysorbate 80 (5% pet.) could not be reproduced.

Discussion

Several cases of an allergic contact dermatitis to Efudix® cream have been reported, either with a reaction to vehicle components, 5-FU (1–5), or serial dilutions or both.

The present study concerns 14 patients, of whom 8 reacted to the active ingredient 5-FU and 4 to a vehicle component of Efudix® cream. There were 2 patients who had positive reactions to propylene glycol and

stearyl alcohol, as well as to different dilutions of 5-FU. All 8 patients with positive reactions to 5-FU also had a positive reaction to Efudix® cream (with one of them only showing a weak reaction to Efudix® cream 1% pet.). The number of patients is too small to predict the most possible positive ingredient if the cream is positive on patch testing.

We were unable to create a control group for patch testing with Efudix® cream. However, 4 out of the 14 patients who were tested, showed no positive reactions. Yesudian and King tested 10 controls simultaneously with 3 patients with allergic contact dermatitis to stearyl alcohol in Efudix® cream. They also tested with the ingredients of Efudix® cream, serial dilutions of 5-FU (0.1%, 1% and 5% in aq.) and serial dilutions of Efudix® cream (0.1%, 1% and 5% in pet.). There were no positive reactions in the 10 controls (1).

Allergic contact dermatitis to 5-FU is infrequent. However, the development of an irritant contact dermatitis is frequently seen. In 1977, Goette and Odom postulated several diagnostic features that may help to distinguish between these reactions. An allergic reaction is more likely if there is (i) development of a severely pruritic eczematous dermatitis at the site of application, (ii) occurrence of a widespread pruritic eczematous eruption at the distant site and (iii) a positive patch test reaction (3). They also reported an allergic contact dermatitis to FU, which developed in 2 patients 8

Table 1. Results of the positive patch tests in the 14 patients suspected for allergic contact dermatitis to Efudix® cream. In patients 2, 5, 9 and 14 all tests were negative

Patients	1	3	4	6	7	8	10	11	12	13
Propylene glycol 20% aqua	2+	neg	neg	neg	neg	neg	neg	neg	neg	3+
Methyl parahydroxybenzoate 3% pet.	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
Propyl parahydroxybenzoate 3% pet.	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
Stearyl alcohol 30% pet.	2+	2+	neg	neg	neg	neg	neg	neg	neg	2+
Polysorbate 80 5% pet.	neg	neg	neg	neg	neg	neg	1+*	neg	neg	neg
Sorbitan monooleate 5% pet.	neg	neg	neg	neg	neg	neg	1+†	neg	neg	neg
Efudix® cream 0.1% pet.	neg	neg	neg	neg	neg	neg	neg	neg	1+	neg
Efudix® cream 1% pet.	2+	neg	1+*	1+†	2+	neg	neg	neg	2+	neg
Efudix® cream (as is)	3+	2+	neg	2+†	2+	2+	neg	2+	3+	3+
5-FU 1 mg/ml saline (0.1%)	neg	neg	neg	neg	neg	neg	neg	neg	neg	2+
5-FU 10 mg/ml saline (1%)	2+	neg	neg	1+†	2+	2+	neg	2+	neg	2+
5-FU 50 mg/ml saline (5%)	3+	neg	2+*	2+†	3+	2+	neg	3+	3+	2+

1+, +; 2+, ++; 3+, +++; neg, negative reaction; 5-FU, 5-fluorouracil.

*Not reproducible.

†Reproducible.

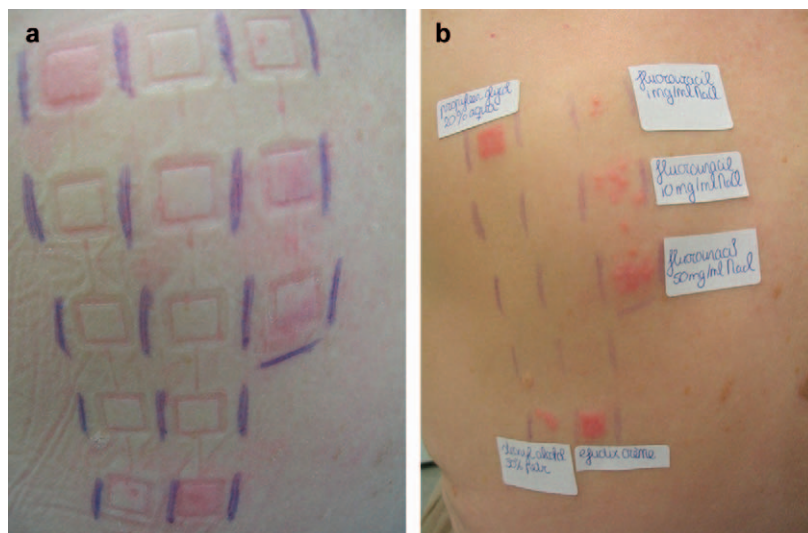


Fig. 1. (a) Patch test reactions in patient 13 at day 2. (b) Patch test reactions in patient 13 at day 4.

and 18 days, respectively, after institution of topical FU therapy. Epicutaneous patch tests and intradermal tests with FU produced positive reactions. 12 control subjects had no reaction to intradermal FU testing (10).

Propylene glycol (PG, 1,2-propanediol) is an emulsifying agent commonly used as a vehicle in topical preparations. Farrar et al. reported 1 case of allergic contact dermatitis to PG in Efudix® cream (2). Stearyl alcohol is an 18-carbon aliphatic alcohol that has low potential for sensitization. A few cases of contact allergic dermatitis to stearyl alcohol in Efudix® cream have been reported (1, 4). Polysorbate 80 (INCI name) is also called Tween 80 and polyoxyethylene sorbitan monooleate. Contact allergy to it is not common, even though it is widely used for the preparation of oil-in-water emulsions in pharmaceutical products, cosmetics, and industrial detergents (11, 12). It can also induce non-specific irritation. Sorbitan monooleate (Span 80) is used as surfactant in many topical agents and belongs to the group of non-ionic emulsifiers. Sensitization to these agents has already been recognized in leg ulcers (13) and contact cheilitis (14).

5-FU is considered a weak sensitizer. The therapeutic inflammation produced by Efudix® cream can probably enhance the penetration through the skin, and probably increase the allergenic potential of

allergen(s) (7). This is more expected of substances already known to be sensitizers (e.g. propylene glycol). Moreover, the duration of treatment may also play a role in sensitization. In our patients, all reactions developed after multiple cycles of treatment with Efudix® cream, except for 1 patient who developed a reaction 10 days after initial treatment.

There is an important clinical consequence for patients with allergic contact dermatitis to 5-FU or the vehicle components of Efudix® cream. This is particularly relevant because most of these patients have multiple actinic keratoses that require treatment. Therefore, other therapeutic modalities should be considered for treating such patients.

We believe that an allergic contact dermatitis to Efudix® cream or 5-FU is not as rare as one was led to believe. Every physician prescribing Efudix® cream should be well aware of the possible consequence of an allergic contact dermatitis. It is useful to test the cream as is and its ingredients to be able to provide an adequate advice for treatment in the future.

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