controlled provocation, was detected and related to SB-containing wine and cheese.9 SB-induced pruritus may also develop due to its use as a food additive.10 In the present case there was no systemic reaction following oral SB intake, but only an acute, transient, urticarial face rash, likely indicating nonimmunologic contact urticaria.

A further work-up with additional patch and prick tests was planned, but could not be performed due to an imbalance in the patient’s metabolic status. Our patient has an important metabolic disease that could become life-threatening if SB treatment were to be discontinued. Therefore, we emphasize the importance of a timely recognition of isolated contact urticaria to SB-containing drugs upon contact with the skin, which does not automatically mean they can no longer be used orally. This way, unnecessary elimination, and/or the use of alternative (potentially lesser effective) drugs, can be avoided.

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Contact allergy to topical diclofenac with systemic tolerance

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Diclofenac (CAS 15307-86-5) is a widely used non-steroidal anti-inflammatory drug (NSAID). In topical formulation, its main application lies in the treatment of actinic keratoses and minor sports injuries such as joint sprains or contusions. Allergic contact dermatitis

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(ACD) after topically applied diclofenac\textsuperscript{1,2} and type IV reactions after oral intake are rarely reported.\textsuperscript{3} To date, no study exists on possible oral tolerance in patients with contact allergy to topical diclofenac. We report two patients with contact allergy to diclofenac and subsequent tolerance in oral challenge tests.

**CASE REPORTS**

The first patient, a 52-year-old man, presented with an ACD on the left hip after topical use of diclofenac gel (11.6 mg/g diclofenac diethylamine; GSK, Munich, Germany) for 2 days (Figure 1A). The second patient, an 81-year-old man, developed facial ACD after 5 weeks of topical application of diclofenac gel (30 mg/g diclofenac sodium; Almirall, Reinbek, Germany) for the treatment of actinic keratoses. In both patients, no earlier reactions to NSAIDs had occurred, but one of the two patients did not remember previous intake specifically of diclofenac. They both underwent patch testing according to the guidelines of the German Contact Dermatitis Research Group (DKG).\textsuperscript{4,5} Patch testing with the DKG baseline and preservative series showed no positive reaction. The individual diclofenac-containing gels were patch tested “as is” and elicited positive reactions (Figure 1B, D). Diclofenac sodium (Chemotechnique, Malmö, Sweden, and an in-house preparation) was patch tested at 1% and 5% pet. and revealed positive skin reactions in both patients after 48 and 72 hours (Figure 1C, E). Ten controls tested negative with these test preparations. Skin prick tests with a diclofenac tablet, diluted in 1 mL NaCl 0.9%, showed negative results in immediate (20 minutes) and late readings (24 hours) in both patient. Subsequent oral challenges following the national guidelines for the diagnosis of drug hypersensitivity\textsuperscript{6} with a maximum single dose of 50 mg diclofenac over 2 days (maximum cumulative dose of 110 mg daily) were well tolerated.

**DISCUSSION**

Topical diclofenac, a phenylacetic acid derivative, has an anti-inflammatory and analgesic effect, mainly due to inhibition of
cyclooxygenases. It is well known that systemic intake of diclofenac may cause either NSAID hypersensitivity or drug-specific allergic reactions, ranging from anaphylaxis to severe delayed hypersensitivity reactions. Positive patch tests containing a 0.75 mg/mL diclofenac sodium solution (vehicle not reported) were described after delayed hypersensitivity reactions (maculopapular eruptions) following oral application, showing negative results in eight control patients. Avoidance of local use of diclofenac is recommended in the case of any previous allergic reaction to systemically applied phenylacetic acid derivatives. This recommendation includes topically applicable ferbinac and aceclofenac, which are structurally related and have been reported to have cross reactivity to diclofenac. Surprisingly, no clinical study has been conducted to validate this recommendation.

The situation in our two patients is just the reverse: our patients tolerated 100 mg diclofenac orally despite proven and extensive previous ACD. Up to now, there are no reports of intolerance reactions to orally used diclofenac after previous ACD due to topical diclofenac. We conclude that contact dermatitis may not necessarily exclude the systemic application of the same compound. It has been hypothesized that “compartment allergies” may be responsible for such findings. Another possible explanation for tolerating systemic use may also be that diclofenac is modified by digestive juices or metabolized and a new epitope/allergen is formed that does not crossreact with the epitope formed in the skin. Since oral challenge tests represent the gold standard in the diagnosis of drug hypersensitivity, we suggest excluding (or proving) systemic allergy by oral challenges in individuals allergic to topical diclofenac.

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The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Caroline Beutner: Conceptualization (lead); data curation (lead); formal analysis (supporting); writing – original draft (lead). Susann Forkel: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal). Katharina Kreipe: Data curation (lead); formal analysis (equal); methodology (equal); writing – original draft (equal). Johannes Geier: Formal analysis (lead); methodology (equal); writing – original draft (equal). Timo Buhl: Conceptualization (lead); methodology (equal); writing – original draft (equal).

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