

the intermediate and the end product, azathioprine, was studied by TLC, as follows. Azathioprine was dissolved in dimethyl sulfoxide (DMSO), and precipitated from the solution with acetone. The solid precipitate was again handled 2× in the same manner. The combined acetone solutions were then evaporated to near dryness, and the residue dissolved in 0.5 ml of DMSO, of which solution 0.65 µl was pipetted onto a TLC silica gel plate (60F₂₅₄, 0.25 mm, E. Merck, Darmstadt). A standard series of AZA III dissolved in DMSO was pipetted beside the analyte, and the plate was developed with a solvent mixture of dichloromethane and hexane (41:59). The retention of AZA III on the plate was 0.4, and the detection limit for a AZA III stain, 1 µg.

In the 1st test session, all patch tests were negative except AZA III, which gave ++ reactions at 10%, 1%, 0.1 and 0.01% pet (Table 1). In the 2nd test session, AZA III gave a + reaction at 0.001% and a ?+ reaction at 0.0001%, and azathioprine gave a ?+ reaction at 10%. Azathioprine tablet (Imurel® 50 mg, 50 mg azathioprine in a tablet weighing 157.5 mg=32%) at 100% and at 50% pet. gave + reactions. In addition, tioconazole, econazole and miconazole, not used by the patient, gave +, + and ?+ reactions at 2% eth., respectively (Table 1). The tests to the imidazole derivatives at 2% pet. were negative. All tests to clotrimazole, ketoconazole and itraconazole at 2% pet. and eth. were negative.

The TLC analyses showed that the intermediate product AZA III contained more than 98% 5-chloro-1-methyl-4-nitroimidazole. Azathioprine was shown to contain at least 8 different impurities. 1 of the fractions (no. 2) was identical to 5-chloro-1-methyl-4-nitroimidazole. The TLC analyses also showed that the azathioprine contained 0.004% 5-chloro-1-methyl-4-nitroimidazole. On patch testing, the patient also reacted to TLC fraction no. 2 (Table 1).

Discussion

Hypersensitivity to systemic azathioprine is well-known (2, 3), and 2 cases of occupational allergic contact dermatitis from azathioprine have been reported (4, 5), but, to our knowledge, contact allergy to 5-chloro-1-methyl-4-nitroimidazole, an intermediate product of azathio-

prine, has not previously been reported. 5-chloro-1-methyl-4-nitroimidazole was shown to be present in the end products, azathioprine and azathioprine tablets, in amounts sufficient to induce allergic patch test reactions in a sensitized patient.

Burden & Beck (4) were aware of 5-chloro-1-methyl-4-nitroimidazole impurity in azathioprine. Their patient gave an allergic patch test reaction to azathioprine diluted to 1% pet. and the test to a 1% dilution of a crushed azathioprine tablet in pet. was strongly positive. Their patient was allergic to azathioprine, but most probably not to 5-chloro-1-methyl-4-nitroimidazole, although patch testing to the pure chemical was not performed. Our patient reacted to 5-chloro-1-methyl-4-nitroimidazole only, not to azathioprine.

Cross-reactivity was found between 5-chloro-1-methyl-4-nitroimidazole and 3 out of 6 imidazole derivatives used as antifungal drugs tested. This confirms the suggestion of Stubb et al. (6) regarding cross-reactivity between various imidazole derivatives.

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Delayed-type hypersensitivity to mofebutazone underlying a severe drug reaction

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Case Report

In January 1992, a then 47-year-old woman started oral treatment for thrombophlebitis with 150 mg mofebutazone

plus 100 mg horse chestnut (Vasotonin® forte) daily and topical heparin (Thrombareduct® gel 60.000). After 3 to 4 days, a patchy erythema developed, which

was partly vesicular and exudative. The eruption began on the abdomen, but then spread to the entire body surface, except for the face and mucous membranes. The medication was discontinued and the eruption cleared with topical corticosteroid treatment. The patient reported that 15 years ago, the topical application of an ointment containing mofebutazone, escin and arnica extract (Vasotonin® Serol) had been followed by a rash restricted to the treated site.

After the eruption had cleared, skin tests were performed. The test material comprised the mofebutazone-containing tablets (Vasotonin® forte; Merz, Frankfurt, Germany) and ointment (Vasotonin® Serol; Merz), the individual constituents of Vasotonin® forte (Merz), aminophenazone, propyphenazone, phenylbutazone, oxyphenbutazone (all obtained from Sigma, Deisenhofen, Germany), and the Thrombareduct® 60.000 gel (Azupharma, Gerlingen, Germany). Prick and patch tests were carried out according to standard methods.

On prick testing, no immediate-type, but a strong delayed reaction of the eczematous type was seen after 2 days to Vasotonin® forte tablets (Table 1). Patch test reactions occurred in a crescendo fashion to Vasotonin® forte tablets and Vasotonin® Serol ointment (Table 2). Testing the individual constituents of the mofebutazone-containing preparation revealed a positive patch test re-

action to mofebutazone only. Further testing elicited a reaction to phenylbutazone, but no reactions to aminophenazone, propyphenazone or oxyphenbutazone.

Comment

Phenylbutazone and oxyphenbutazone are known elicitors of hypersensitivity reactions: they may both cause immediate-type reactions up to anaphylactoid shock (1) or delayed-type reactions like exanthema (2–4). In the most severe cases, erythroderma, exfoliative dermatitis, widespread erythematous bullous reactions or toxic epidermal necrolysis may occur (5, 6). To our knowledge, no hypersensitivity reactions to mofebutazone have so far been reported. Interestingly, reactions to mofebutazone were not only found on patch testing, but also prick testing in this patient. Sensitization may have been induced by prior topical application of an ointment containing mofebutazone. In view of the blistering eruption upon ingestion of Vasotonin® forte tablets, we did not risk an oral challenge test with mofebutazone. Some studies have revealed cross-sensitization between various pyrazolone derivatives on patch testing (3, 7). Therefore, despite the negative patch tests to aminophenazone and propyphenazone, the patient was advised to avoid all pyrazolone derivatives in view of the risk of severe clinical reactions due to possible cross-reactivity.

Table 1. Results of prick tests

	20 min	D1	D2
Vasotonin forte® Tablet ^{a)}	–	n.d.	dermatitis with blisters ^{b)}

^{a)} Tablets were crushed and suspended in physiological saline.

^{b)} No reaction in 10 controls.

Table 2. Results of patch tests

	D2	D3	D4
Vasotonin® forte tablet ^{a)}	+++ ^{b)}	+++ ^{b)}	n.d.
mofebutazone 1% pet.	+ ^{b)}	+++ ^{b)}	n.d.
Vasotonin® Serol ointment as is	+ ^{b)}	+++ ^{b)}	n.d.
all other individual constituents of Vasotonin® forte tablets, except mofebutazone	–	–	n.d.
phenylbutazone 1% pet.	–	+ ^{b)}	++ ^{b)}
oxyphenbutazone 1% pet.	–	–	–
aminophenazone 1% pet.	–	–	–
propyphenazone 1% pet.	–	–	–
Thrombareduct® gel as is	–	–	–

^{a)} Tablets were crushed and moistened with tap water.

^{b)} No reaction in 10 controls.

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