

## Cutaneous reactions to captopril

### Predictive value of skin tests

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### Summary

Cutaneous reactions associated with captopril treatment occurred in fifteen out of eighty-nine patients (17%). Dose reduction invariably led to improvement of the reaction but later recurrences were frequent (six patients). In four out of the fifteen patients captopril withdrawal ultimately was necessary. Skin tests and *in vitro* lymphocyte transformation tests with captopril were performed in these fifteen patients and also in nine captopril-treated control patients without adverse reactions.

Positive epicutaneous skin tests were observed in five out of the fifteen patients including the four in whom captopril had to be withdrawn, but in none of the controls. Intracutaneous skin tests were positive in ten of the patients with cutaneous reactions and in two control patients. Captopril-induced *in vitro* lymphocyte transformation occurred in most patients with cutaneous reactions whereas in control patients captopril suppressed the *in vitro* lymphocyte proliferative response. Skin biopsies revealed histologic changes consistent with lymphocytic vasculitis.

We conclude that epicutaneous skin tests with captopril are helpful in predicting the necessity of captopril withdrawal.

### Introduction

The angiotensin-1 converting enzyme inhibitor captopril has become a valuable drug in the treatment of severe hypertension, especially in patients resistant to combinations of other antihypertensive agents (Editorial, 1980). Cutaneous reactions, the most common side-effect of captopril, are reported to subside spontaneously or after dose reduction (Wilkin, Hammond & Kirkendall, 1980). However, in our experience recurrence of cutaneous reactions, even after dose reduction, is frequent and necessitates captopril withdrawal in a substantial number of patients (Hoorntje, 1981).

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In this report we describe the frequency and nature of skin reactions observed in eighty-nine captopril-treated patients who were studied prospectively. We present the results of skin testing with captopril and the results of *in vitro* lymphocyte transformation tests with the drug in patients with and without skin reactions. The clinical usefulness of the epicutaneous skin test in predicting the ultimate outcome of this adverse reaction to captopril and its pathogenesis are discussed.

## Materials and methods

### *Patients*

Eighty-nine hypertensive patients were treated with captopril for periods lasting from 6 months to 2.5 years with an average treatment period of 17 months. Mean age of the patients was 42 years (s.d. 12), ranging from 18 to 65 years. There were fifty-seven males and thirty-two females. Mean captopril dose after 1 month of treatment was 240 mg daily with a range of 37.5–450 mg daily. After withdrawal of previous antihypertensive medication, captopril was initiated and titrated step by step in weekly intervals. Subsequently, the patients were examined monthly and asked for possible side-effects at each visit.

A cutaneous lesion was considered to be induced by captopril, when it developed newly and where no other agents could be held responsible. Thus, two patients were excluded from this study because the involvement of other drugs in the cutaneous reaction was considered possible. When a cutaneous reaction to captopril had developed, the dose of the drug was reduced. After the skin lesions had subsided, captopril dose was increased again when blood pressure could not be adequately controlled with the lower dosage. Captopril was withdrawn when reappearing cutaneous lesions did not improve after a new dose reduction.

Epicutaneous and intracutaneous skin tests and *in vitro* lymphocyte transformation tests were performed in all patients with a cutaneous reaction to captopril after the skin lesions had subsided completely; moreover in some patients immediately after the cutaneous reaction had developed. Skin biopsies of affected areas were performed in three of the patients. Skin tests and lymphocyte transformation tests were also done on a group of nine captopril-treated patients without adverse reactions during any time on captopril. Blood for lymphocyte transformation tests was always collected before the skin tests.

### *Skin tests*

Epicutaneous skin tests were performed with pure captopril mixed with vaseline in concentrations of 0.1, 1 and 10%, applicated on the back of the patient, according to the description by Bandmann and Dohn (1967). Reactions were observed 48 and 72 hr later by a trained nurse. A reaction was considered to be positive when at least erythema and oedema or a papular reaction was present.

Intracutaneous test solutions were made by solving pure captopril in a Coca solution in concentrations of 0.1, 1 and 10 mg/ml (solutions with Coca only and with Coca and histamine 0.01 mg/ml were used as controls; 0.05 ml of the solutions were injected intracutaneously on the volar side of the arm. Reactions were observed by a trained nurse 15 min after injection. The test was considered to be positive when wheals or flares at the site of the injection with the captopril solution equalled or exceeded that with histamine.

*Lymphocyte transformation tests*

For the lymphocyte transformation tests peripheral blood mononuclear cells were obtained from fresh heparinized blood by Ficoll-Isopaque density gradient centrifugation. Cells,  $10^5$ /well, were cultured on microtitre plates in RPMI 1640 medium supplemented with 20% pooled allogeneic human serum and captopril in concentrations of 3, 10, 30 and 300  $\mu\text{g/ml}$  for 6 days. Control cultures without captopril were included. Stimulation was determined as the uptake of [ $^3\text{H}$ ]-thymidine ([ $^3\text{H}$ ]TdR) during the last 16 hr of culture (Kallenberg, de Gast & The, 1980). Results are expressed as stimulation index (SI)—i.e. mean disintegrations per minute (dpm) per culture with captopril as stimulant divided by mean dpm of the culture without the drug.

**Results**

Fifteen out of eighty-nine patients (17%) developed a cutaneous reaction to captopril. Clinical characteristics are given in Table 1. Age, sex and captopril dose were not significantly different from those of the total patient population. Cutaneous reactions developed at a mean period of 5 weeks after the onset of captopril therapy. This period ranged from immediately after the first dose of captopril up to 12 weeks after the start. The rash was in general maculopapular ( $n=7$ ) or urticarial ( $n=7$ ) in character. Histologic examination performed in three patients revealed changes consistent with lymphocytic vasculitis with perivascular infiltrates of lymphocytes and eosinophils and extravasation of erythrocytes subepidermally (Fig. 1). Accompanying symptoms occurred in eight patients and included angioneurotic oedema, fever, arthralgia, loss of taste and alopecia.

In all patients initial improvement was seen after dose reduction. In eleven patients

**Table 1.** Clinical characteristics of patients with captopril-induced cutaneous reactions

| Patient (No.) | Age (year) | Sex | Daily dose of captopril (mg) | Weeks between start of captopril and onset of skin lesions | Type of rash* | Accompanying symptoms† | Relapse | Withdrawal |
|---------------|------------|-----|------------------------------|------------------------------------------------------------|---------------|------------------------|---------|------------|
| 1             | 57         | M   | 450                          | 5                                                          | u             | f,a,p                  | +       | +          |
| 2             | 59         | M   | 150                          | 6                                                          | m             | —                      | +       | +          |
| 3             | 51         | M   | 400                          | 12                                                         | m             | —                      | +       | +          |
| 4             | 37         | F   | 75                           | 2                                                          | m             | an                     | +       | +          |
| 5             | 36         | F   | 200                          | 9                                                          | m             | —                      | —       | —          |
| 6             | 39         | F   | 300                          | 1                                                          | u             | f,m                    | —       | —          |
| 7             | 45         | M   | 450                          | 2                                                          | m             | f                      | —       | —          |
| 8             | 49         | F   | first dose                   | 0                                                          | u             | —                      | —       | —          |
| 9             | 32         | M   |                              | 6                                                          | u             | a                      | +       | —          |
| 10            | 47         | M   | 300                          | 3                                                          | m             | —                      | +       | —          |
| 11            | 64         | M   | 100                          | 5                                                          | m             | —                      | —       | —          |
| 12            | 40         | M   | 150                          | 1                                                          | u             | an                     | —       | —          |
| 13            | 44         | F   | 400                          | 8                                                          | u             | —                      | —       | —          |
| 14            | 21         | M   | 150                          | 6                                                          | u             | f,a                    | —       | —          |
| 15            | 65         | M   | 450                          | 8                                                          | l             | al,t                   | —       | —          |

\* u = urticarial, m = maculopapular, l = lichenoid.

† f = fever, a = arthralgia, p = proteinuria, an = angioneurotic oedema, m = myalgia, al = alopecia, t = taste loss.

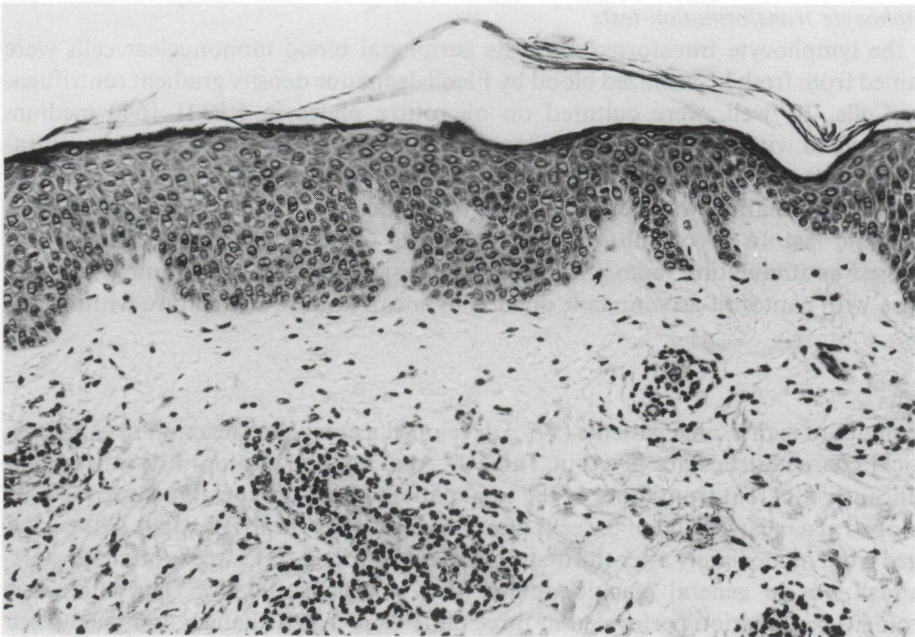


**Fig. 1.** Skin biopsy specimen of clinically involved skin in captopril-associated rash. (Haematoxylin-Eosin staining, magnification  $\times 140$ .) Perivascular lymphocytes and eosinophils and extravasation of erythrocytes are present subepidermally.

the skin lesions disappeared completely, in most of them within a few days. In the four remaining patients the cutaneous lesions worsened again, whereas in two patients skin eruptions reappeared after a symptom-free period. In four of these six patients captopril had to be withdrawn eventually 1–2 months after the rash had developed. Neither the type of cutaneous reaction nor the presence of accompanying symptoms were associated with a particular course of the skin lesions.

**Table 2.** Epicutaneous and intracutaneous skin tests in patients with captopril-induced cutaneous reactions and in captopril-treated patients without adverse reactions. Lowest concentrations with a positive reaction are represented.

|                                          | Epicutaneous skin tests |    |      | Intracutaneous skin tests (mg/ml) |   |     |
|------------------------------------------|-------------------------|----|------|-----------------------------------|---|-----|
|                                          | 10%                     | 1% | 0.1% | 10                                | 1 | 0.1 |
| Patients with cutaneous reactions (n=15) | 0                       | 5  | 0    | 2                                 | 6 | 2   |
| Withdrawal of captopril (n=4)            | 0                       | 4  | 0    | 0                                 | 3 | 1   |
| Control patients (n=9)                   | 0                       | 0  | 0    | 2                                 | 0 | 0   |

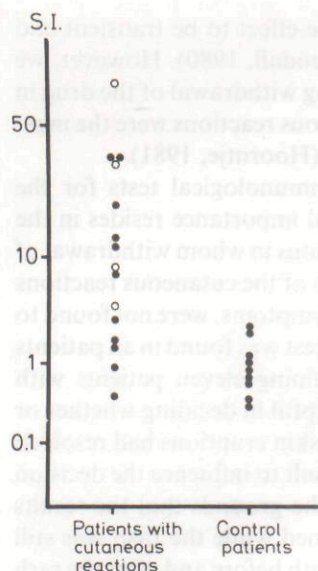


Fig. 2. Lymphocyte stimulation index (SI) to captopril in patients with cutaneous reactions to captopril as compared with captopril-treated patients without adverse reactions. The difference between the two groups is statistically significant ( $P < 0.01$ , paired Student *t*-test). Open circles represent the patients in whom captopril was withdrawn.

Epicutaneous skin tests with captopril were positive in five out of the fifteen patients with cutaneous reactions and negative in all control patients without adverse reactions (Table 2). A significant association between a positive epicutaneous skin test and the necessity of captopril withdrawal was found, as the test was positive in all the four patients in whom captopril had to be withdrawn ( $P < 0.01$ ;  $\chi^2$  analysis). The fifth patient with a positive test was a female with scleroderma.

Intracutaneous skin tests were positive in ten of the patients with cutaneous reactions, including all those with recurrent skin lesions. In the nine patients without adverse reactions, two showed a positive reaction to the highest concentration of intracutaneously administered captopril (Table 2). There was a significant correlation between positive intracutaneous tests and the occurrence of a relapse ( $P < 0.05$ ;  $\chi^2$  analysis).

*In vitro* lymphocyte transformation with captopril as an antigen in a concentration of  $30 \mu\text{g}/\text{ml}$  resulted in stimulation in patients with a cutaneous reaction to captopril. In all of the patients with a relapse of the side-effect a stimulation index of 2 or more was observed. In contrast, in half of the patients without adverse reactions suppression of spontaneous lymphocyte transformation ( $\text{SI} < 1$ ) was observed on addition of captopril to the medium (Fig. 2). There was a significant difference in SI between the patients with a cutaneous reaction and the control patients ( $P < 0.01$ ).

## Discussion

Cutaneous reactions form the most frequent side-effect in captopril treatment and are reported to occur in approximately 10% of the patients (Vidt, Bravo & Fouad, 1982). In our population, captopril-associated cutaneous reactions occurred in fifteen out of

eighty-nine patients (17%). Most reports describe this side-effect to be transient and responsive to dose reduction (Wilkin, Hammond & Kirkendall, 1980). However, we found this adverse reaction to be more serious, necessitating withdrawal of the drug in four of our patients. In fact, along with proteinuria, cutaneous reactions were the most frequent reason to withdraw captopril in our population (Hoorntje, 1981).

Apart from the significance of the results of the immunological tests for the pathogenesis of captopril-induced skin lesions, the clinical importance resides in the possibility of detecting those patients with cutaneous reactions in whom withdrawal of the drug will prove to be necessary. Clinical characteristics of the cutaneous reactions to captopril such as the type of rash or the accompanying symptoms, were not found to be useful in this respect. Since a positive epicutaneous skin test was found in all patients with captopril withdrawal and in only one of the remaining eleven patients with cutaneous reactions, we conclude that this test may be helpful in deciding whether or not to withdraw captopril. Tests were performed after the skin eruptions had resolved or captopril was withdrawn, thereby preventing the test result to influence the decision to continue or withdraw the drug. One might object on the grounds that the results could have been different when the test had been performed while the rash was still present. However, in some patients tests were performed both before and after the rash had resolved, and yielded identical results.

Due to insufficient specificity, intracutaneous skin tests were not found to be clinically useful in predicting recurrence of the rash or the necessity to withdraw the drug. As far as the lymphocyte transformation test was concerned, a high SI ( $> 2$ ) was only found in 73% of patients with skin lesions due to captopril. Because of lack of sensitivity and specificity this test seems neither helpful to detect the inducing role of captopril in cutaneous reactions of doubtful aetiology, nor in predicting the necessity of captopril withdrawal.

Besides their clinical usefulness, our data may shed light on the pathogenesis of captopril-induced skin reactions. Histological examination revealed lymphocyte perivascular infiltration, consistent with a cellularly mediated immune reaction. The positive *in vitro* lymphocyte transformation tests with the drug and the positive epicutaneous tests are in accordance with such a mechanism. Especially in patients with relapsing cutaneous reactions that eventually necessitate captopril withdrawal, an immunologic memory to captopril may have developed resulting in positive epicutaneous skin and *in vitro* transformation tests, and a strong *in vivo* cutaneous reaction after renewed contact with the drug. However, the positive intracutaneous tests and the infiltration with eosinophils suggest that immediate type hypersensitivity reactions may also play a role. The occurrence of these latter reactions in patients without relapsing skin reactions suggests that they are of minor importance in the residing 'clinical hypersensitivity' to captopril.

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