action of phosphine in man is not known. It has, however, been found to cause non-competitive inhibition of cytochrome oxidase of mitochondria in mouse liver, housefly, and granary weevil.1

Since the mortality is so high and there is no specific antidote, we suggest that a less toxic but equally effective agent should be sought to replace this lethal substance.


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Severe cutaneous reactions to captopril

Captopril is an angiotensin converting enzyme inhibitor used to treat hypertension and cardiac failure. Cutaneous reactions to captopril are common, occuring in about 12% of patients treated for hypertension,2 and generally thought to be mild and self limiting; they include angio-oedema, a pruritic maculopapular eruption, a rash resembling pityriasis rosea,3 mild toxic erythema,4 and exfoliative dermatitis.5 None of these reactions was confirmed by challenge. We recently saw a more serious and extensive pattern of eruption develop during treatment of cardiac failure with small doses of captopril.

Case reports

The table gives details of the four patients reported on.

Case 1—A 59 year old woman was given captopril, up to 75 mg daily, for cardiac failure. After two weeks she developed a pruritic macular eruption, which settled without change in treatment. Four weeks later a scaling erythema that began on her hands and face led to erythroderma. Captopril was withdrawn, and after six weeks the eruption had settled. A challenge dose of captopril 12.5 mg reproduced the eruption in four days, which resolved in two weeks. Her heart failure was subsequently controlled by enalapril.

Case 2—A 57 year old man with insulin dependent diabetes was given captopril 75 mg daily for cardiac failure. After six weeks he developed an urticated scaling erythema of the hands and face that extended to other areas. This lasted for six weeks despite withdrawal of captopril. A challenge dose (12.5 mg) exacerbated the eruption, which resolved in two weeks.

Case 3—An 80 year old man with cardiac failure received captopril, up to 75 mg daily. Three weeks later he developed an exanthematous eruption of the hands and arms that led to erythroderma and persisted for four weeks despite withdrawal of captopril. His other treatment was not changed. He died of uncontrollable cardiac failure shortly afterwards.

Case 4—A 63 year old man with cardiac failure was given captopril 75 mg daily. He developed an urticated erythema four weeks later. Aloppurinol, which had been taken for two years, and captopril were stopped. The eruption persisted for two weeks, and he died soon afterwards. The pattern and course of his skin eruption strongly implicated captopril.

Comment

These cases show stages of the same eruption, characterised by an urticated erythema with eczematous features leading to erythroderma. The delayed onset, relentless progression, and intractability of the eruption after withdrawal of captopril were consistent features. A single challenge dose of 12.5 mg reproduced the reaction. Biopsy showed acute or acute on chronic dermatitis with perivascular inflammation. Immunofluorescence studies yielded negative results.

This pattern of eruption was different from those previously described, which were thought to be pharmacological in nature, probably due to inhibition of inflammatory mediator metabolism by angiotensin converting enzyme, and were dose related.6

This new eruption seems to be a truly allergic response to captopril reproducing with one dose and not dose related. The patient with impaired renal function, but even so captopril 75 mg daily is not a high dose, although delayed clearance may have contributed to the intractability of the eruption. The delayed pattern of onset suggests a photosensitive element, and as the patients were receiving several drugs in interaction with captopril was also possible. All these factors may have affected the final pattern of eruption, and the sulphydryl group of the captopril molecule, not present in enalapril, may have been the allergenic focus, as has been previously suggested.7

We believe that these four cases show a new, severe pattern of erythema to the captopril as used to treat cardiac failure. If the potential of angiotensin converting enzyme inhibitors is to be exploited in the next five years8 we must be sure that each new therapeutic indication is not accompanied by a new, more serious side effect.


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Details of four patients with skin eruption after treatment with captopril up to 75 mg daily

<table>
<thead>
<tr>
<th>Age (years) and sex</th>
<th>Eruption</th>
<th>Time course of eruption</th>
<th>Duration of captopril treatment</th>
<th>Other drugs (daily doses)</th>
<th>Abnormal biochemical results (mmol/l)</th>
<th>Result of challenge</th>
<th>Result of biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>59 F</td>
<td>Erythroderma</td>
<td>Onset six weeks after captopril started. Lasted six weeks after withdrawal</td>
<td>4 months</td>
<td>Frusemide 120 mg Warfarin</td>
<td>Urea 11.3 Creatinine 183 Positive (but no recurrence with enalapril)</td>
<td>Acute on chronic dermatitis with infiltrate of polymorphs and eosinophils. No immunofluorescence</td>
<td>Acute cutaneous dermatitis with polymorphonuclear infiltrate. No immunofluorescence</td>
</tr>
<tr>
<td>57 M</td>
<td>Urticated erythema</td>
<td>Onset six weeks after captopril started. Lasted six weeks after withdrawal</td>
<td>2 months</td>
<td>Frusemide 120 mg</td>
<td>Urea 13.8 Creatinine 190 Positive</td>
<td>Acute cutaneous dermatitis with polymorphonuclear infiltrate. No immunofluorescence</td>
<td>Acute dermatitis with perivascular eosinophilic infiltrate. No immunofluorescence</td>
</tr>
<tr>
<td>80 M</td>
<td>Erythroderma</td>
<td>Onset three weeks after captopril started. Lasted four weeks after withdrawal</td>
<td>4 weeks</td>
<td>Frusemide 120 mg</td>
<td>Urea 23.1 Creatinine 428</td>
<td>Patient died before challenge</td>
<td>Acute cutaneous dermatitis with perivascular eosinophilic infiltrate. No immunofluorescence</td>
</tr>
<tr>
<td>63 M</td>
<td>Urticated erythema</td>
<td>Onset four weeks after captopril started. Lasted two weeks after withdrawal</td>
<td>5 weeks</td>
<td>Frusemide 250 mg Hydralazine 75 mg Digoxin 0.125 mg Warfarin Allopurinol 200 mg</td>
<td>Urea 19.3 Creatinine 211</td>
<td>Patient died before challenge</td>
<td>Acute cutaneous dermatitis with perivascular eosinophilic infiltrate. No immunofluorescence</td>
</tr>
</tbody>
</table>

Conversion: SI to traditional units—Urea: 1 mmol/l = 6 mg/100 ml Creatinine: 1 mmol/l = 11.3 mg/100 ml

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