SEVERE SIDE-EFFECTS OF CAPTOPRIL IN ADVANCED CHRONIC KIDNEY INSUFFICIENCY

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Summary

Using equal or lower than manufacturer’s recommended doses of Captopril in 10 hypertensive patients with creatinine clearance less than 30ml/min severe side-effects were observed in four cases. The adverse reactions continued after stopping the drug. One case developed symptomatic thrombocytopenia; one other, a lethal infected exfoliative dermatitis and an irreversible deterioration of her renal function. The other two cases demonstrated severe aggravation of their CRF, one requiring dialysis. The protective effect of dialysis against these side-effects is obvious in this series and dialysis may also accelerate the resolution of the complications. Suggestions for the management of this kind of patient with Captopril are made.

Introduction

Captopril (Capoten®, Squibb) is the only orally effective converting enzyme inhibitor available on the North American market and has proved an extremely potent antihypertensive drug, succeeding in controlling resistant hypertension, especially those types mediated by the renin-angiotensin system [1]. It is mainly eliminated by the kidney with an elimination rate constant which closely parallels the endogenous creatinine clearance (Ccr) [2]. Guidelines for adjusting the dose interval in patients with chronic renal failure (CRF) have been suggested [1]. Theoretically, similar plasma concentrations can be obtained by proportionately decreasing the individual Captopril dose [2].

A rather high incidence of troublesome, or even serious side-effects have been associated with Captopril. There is a general impression [see 1, pages 438–439] that the incidence of adverse effects is significantly lower if patients with renal dysfunction are excluded from statistical studies.

The present paper confirms the impression that advanced CRF patients are particularly prone to develop severe side-effects to Captopril and discusses the alterations of dosage in this category of patients.
Material and methods

Ten patients with advanced CRF (C_cr ≤ 30 ml/min) of different causes have been treated with Captopril in the last year. Two of them were on chronic haemodialysis when Captopril was started: a third patient was on acute peritoneal dialysis for a probable acute interstitial nephritis, presumably secondary to chlorothalidone.

The dosage of Captopril varied between 12.5 mg every 48 hours to 25 mg b.d., with the exception of one patient who required a dose of 50 mg t.i.d. for good hypertension control. In half the cases, including the three being dialysed, all other antihypertensive drugs could be stopped, either before or immediately following the introduction of Captopril.

In the remaining five patients, three also received adjusted doses of frusemide, while the other two needed in addition a beta-blocker or clonidine. During the admission period, the blood pressure was measured regularly in supine and upright positions every half-hour for the first interval of two hours following the administration of Captopril, and subsequently every two hours. Plasma creatinine (P_cr), urea, Na, K, liver function tests, Hb, white cell count and urinalysis were checked at least every other day.

During the initial outpatient period the same tests were performed at ten day intervals for one month and then at longer intervals, depending on the degree of blood pressure control on each patient.

**TABLE I. Description of cases which presented major side-effects**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnostic</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>M</td>
<td>Repeated acute pulmonary oedema. Severe, resistant, renovascular hypertension (frusemide, minoxidil, clonidine, metoprolol, hydralazine, methyldopa). CRF (P_cr = 360 μmol/ml, C_cr = 10.3 ml/min). Nephrotic syndrome of unknown aetiology (proteinuria = 1.5–2.7 g/day). Complex haematological disorder: haemolytic anaemia, thrombocytopenia (80–94,000/μl), circulating anticoagulant, Raynaud syndrome. Autopsy (five months later): bilateral renal artery stenosis, nephrosclerosis. No aetiology found for the nephrotic syndrome and the haematological disorder.</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>F</td>
<td>Acute pulmonary oedema. Severe, resistant hypertension (pindolol, chlorothalidone, nitrpide, frusemide, clonidine, methyldopa). CRF (P_cr = 202 μmol/ml, C_cr = 29 ml/min) with recent acute exacerbation, necessitating peritoneal dialysis (probably acute interstitial nephritis). Autopsy (80 days later): nephrosclerosis, no renal artery stenosis.</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>F</td>
<td>Acute pulmonary oedema. CRF (P_cr = 325 μmol/ml, C_cr = 14.8 ml/min). Severe, resistant hypertension (frusemide, hydralazine, clonidine). Severe congenital immunodeficiency syndrome (2.5% gamma globulin, 3600 leucocytes/μl. Autopsy (10 months later): no renal artery stenosis.</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>F</td>
<td>Acute pulmonary oedema. Severe, resistant hypertension (frusemide, nitrpide). CRF (P_cr = 228 μmol/ml, C_cr = 23.9 ml/min). Chronic pyelonephritis.</td>
</tr>
<tr>
<td>Patient No.</td>
<td>$P_c$ ($\mu$mol/ml)</td>
<td>$C_r$ (ml/min)</td>
<td>Dosage</td>
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<tr>
<td>------------</td>
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</tr>
<tr>
<td>1.</td>
<td>413.6</td>
<td>9.0</td>
<td>12.5mg every 48 hr for 9 days</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>2.</td>
<td>536.8</td>
<td>11.0</td>
<td>12.5mg b.d. x 3d</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>25mg b.d. x 49d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.5mg b.d. x 9d</td>
</tr>
<tr>
<td>3.</td>
<td>440.0</td>
<td>10.9</td>
<td>12.5mg b.d. x 10d</td>
</tr>
<tr>
<td>4.</td>
<td>228.0</td>
<td>23.9</td>
<td>25mg b.d. x 1d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25mg t.d.s. x 3d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50mg t.d.s. x 2d</td>
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</tbody>
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* $P_c = 996\mu$mol/ml, the 10th day. Ten days later 633µmol/ml, but 2 days after 472µmol/ml.
† Three days later, $P_c = 281\mu$mol/ml, but 4 months later 211µmol/ml. Two haemodialyses were required: on the 9th and the 11th day after stopping Captopril.
Results

Six patients did not show any adverse effects which could be associated with Captopril, except for a significant increase of plasma K (from 3.7 ± 0.3 to 4.6 ± 0.6mEq/L). Both haemodialysis patients were in this group.

The four other patients had severe adverse effects most probably related to Captopril. All are described in some detail in Tables I and II.

Discussion

Despite the use of well-adjusted Captopril dosage [1, 3], the incidence and severity of side-effects were rather high in this series: oligoanuria was present in three (requiring dialysis in two), rashes in two (with one case evolving into a severe lethal exfoliative dermatitis), mild leucopenia in two with severe symptomatic thrombocytopenia in one case and possible exacerbation of pre-existing proteinuria in one of the cases. This observation is notably in contrast with the good tolerance of full Captopril dosage in patients with equivalent or more advanced CRF (see 1, Table I). Also it contrasts with the results of one other study [4], where major side-effects were observed only in patients with advanced CRF treated with a full dose of Captopril.

We are not aware of any other report of symptomatic thrombocytopenia (blood pressure in our patient was normal on the day of the epistaxis). Thrombocytopenia was encountered only in 11 of 6000 cases [5]. It is worth mentioning that this patient’s platelet count was abnormally low even before Captopril and he had a rather complex haematological disorder.

Surprisingly, another patient suffering from a congenital immunodeficiency syndrome with leucopenia did not develop thrombocytopenia. In her, only a slight decrease was noted in the leucocyte count.

Exfoliative dermatitis as a side-effect of Captopril has only been reported once previously [6]. The significantly increased proteinuria appeared too early (in this one case of nephrotic syndrome of undetermined aetiology) to be attributed to Captopril. The frequent deterioration of renal function is too severe to be attributed simply to blood pressure reduction. In the medical literature such severe renal deterioration is considered specific for cases of bilateral renal artery stenosis [7]. In our study, however, the only case presenting with this condition (case 1) showed progressive improvement in kidney function during Captopril administration. In another patient (case 3), a similar improvement was observed in the first five days of treatment, preceding a subsequent severe deterioration. In fact, most of the published experimental and clinical studies found an increase of renal plasma flow and glomerular filtration rate, even in acute renal failure experiments [see 1, page 422]. Most probably the severe deterioration of renal function observed in this series (two of three patients needing dialysis) had an organic basis, either a nephrotoxic or an allergic one. The association of significant eosinophilia in two cases favours the latter aetiology, even though no eosinophils were found in the urine. Perhaps the third case, whose eosinophil count increased from 36/µl to 189/µl, was not able to produce an absolute eosinophilia due to her congenital immunologic disease.
The fact of a delay in blood pressure increase after the side-effects resolved (suggesting that enough Captopril persisted in the circulation) seems to us against the hypothesis that an elevated plasma kinin concentration [see 3, page 33] is responsible for some side-effects (rashes).

The resolution of some side-effects of Captopril in spite of continuation of the treatment, as well as the protective effect of dialysis, are against an allergic mechanism, whereas the coincidence between dialysis and restoration of renal function of case 4 favours a nephrotoxic mechanism.

We have already concluded [8] that in CRF patients Captopril should be started at the lowest possible dose (12.5mg) and, if it proves effective, should not be repeated before a significant increase in blood pressure occurs. The interval for the administration of Captopril can be clearly determined in this manner. Once the dose and interval are established, loss of blood pressure control means, in most of the cases, an unrecognised salt and water retention. The addition or increase in dosage of a diuretic will re-establish the effectiveness of the given dose of Captopril.

Recent studies [9] showed almost a similar effectiveness of a dose of 150mg t.d.s. and of 25mg t.d.s. of Captopril in resistant hypertension associated with CRF, even if the same doses of diuretic are maintained. This means higher dosage adds mostly toxic effects with very little benefit on blood pressure control.

Considering the present experience, we are in favour of adding another antihypertensive drug to the combination of diuretic and Captopril rather than increasing the dose above 25mg b.d. in patients with $C_{CR}$ less than 30ml/min, or 12.5mg b.d. in patients with $C_{CR}$ less than 10ml/min.

The dialysance of Captopril, evaluated at 65 per cent of $C_{CR}$ [10], could be a good means for rapidly correcting its side-effects after stopping the drug. Despite the high dialysance of Captopril we did not have to add the equivalent of 50 per cent of the regular dose after each dialysis, as recommended by others [see 3, page 35], probably because ultrafiltration rendered our patients more sensitive to Captopril. This suggests that smaller doses may be effective in well dehydrated patients.

Conclusions

1. Even the present recommended dose of Captopril in CRF patients can produce a high incidence of major side-effects.

2. For this reason the lowest possible dose should be tried initially and, if effective, should not be repeated until a significant increase in blood pressure occurs.

3. If not effective, the dose can be increased, but not above a 'reasonable' amount. There is the possibility that unresponsiveness to rather large doses of Captopril may be due to insufficient dehydration.

4. In any event, before the pharmacodynamics and the pharmacokinetics of Captopril in CRF are better known, it seems preferable to add to the combination of diuretic and Captopril another antihypertensive drug, rather than increasing the dose of Captopril.
References

4. Isles CG, Hodman GP, Robertson JJS. Lancet 1983; i: 355
5. Cooper RA. Arch Intern Med 1983; 143: 659

Open Discussion

MANN (Heidelberg) Regarding the first case with haemolytic anaemia, increased creatinine, severe hypertension and thrombocytopenia did you consider a diagnosis of haemolytic uraemic syndrome?

BERONIADE The case was well studied during the episode and five months after the thrombocytopenia she died and we had an autopsy. We did not find any aetiology either for the nephrotic syndrome or the haematological problem. It was certainly not a case of haemolytic uraemic syndrome.

ANDREUCCI (Naples) I am afraid that you don't have renal biopsies on these patients.

BERONIADE But we have, some months later, autopsies in three of the patients.

ANDREUCCI And what did you find?

BERONIADE As I told you, the first patient died five months after, and this was the only one in whom we confirm a bilateral stenosis of the renal artery. The second one was exfoliative dermatitis which infected the skin.

ANDREUCCI What was the renal histology?

BERONIADE Only nephrosclerosis in the second case, and in the third the autopsy took place six months later and there was diabetic nephropathy.

ANDREUCCI You know that there are two kinds of acute renal failure after Captopril. One is acute interstitial nephritis of the immunological type; this can happen with many drugs and it has been described after Captopril*. The other type has been reported in patients with one functioning kidney and renal

artery stenosis and in patients with bilateral renal artery stenosis. Two articles have appeared recently in the *New England Journal of Medicine*. It was considered as a functional renal failure and attributed to inhibition of angiotensin-induced vasoconstriction of the efferent glomerular arteriole. While I agree on the functional type of acute renal failure I disagree on the suggested mechanism because we have proven that angiotensin II exerts its vasoconstrictive effect only on the afferent arteriole. I personally think that the functional renal failure occurring after Captopril administration is due to salt depletion because Captopril is usually given with diuretics. Captopril itself may cause natriuresis since it stimulates prostaglandin release and prostaglandins are known to cause salt excretion. As a matter of fact the effect of Captopril on blood pressure is immediate whereas the decrease in renal function occurs later after many days and it returns to normal as soon as Captopril administration is discontinued. We have observed this in a young transplant patient with renal artery stenosis; acute renal failure occurred on two occasions both times after several days of Captopril therapy and in both occasions it was reversed by discontinuation of Captopril.

BERONIADE  I know very well your quoted article about the renal function disturbances in patients with bilateral renal artery stenosis treated with Captopril, but as was presented in the paper the only case who has this condition in our series did not have any trouble with his kidney function. Secondly I don't think that the deterioration of kidney function was only on a 'functional' or a pre-renal basis because as you could see in the last case acute renal failure lasted for 14 days and needed two haemodialyses before renal function started again. So I think the renal insufficiency has an organic basis, but of course I cannot say whether the lesion was an acute interstitial nephritis or an acute tubular necrosis.

MORGANTI (Milan)  I understand that in some of your patients blood pressure remained low or returned to normal after stopping the drug for several days, in one case 21 days. Now did you try to evaluate, during this period, whether the classical mechanism responsible for the blood pressure is still active, I mean the blockade of angiotensin II by measuring, for instance, plasma renin activity?

BERONIADE  In two cases we measured the plasma renin activity. In one case about six days and in the other case about 10 days after stopping the drug. The blood pressure was at that time under control and the renin was very high.

MORGANTI  So there was still active blockade of angiotensin?

BERONIADE  Yes. I think we can say that.

EL MATRI (Tunis, Tunisia)  In our experience we have observed four cases of leucopenia in renal insufficiency patients. One case was pancytopenic but in the three others we observed an increase of white blood count one or two days after


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discontinuing treatment. In these patients, who again developed leucopenia on Captopril, we continued the treatment on a dose of 50–100mg daily and observed a quick return to normal of the white blood count. We think they were not cases of haematological toxicity but a new distribution of white blood cells by some effect of Captopril. Have you observed such a phenomenon?

LEVER (Chairman) Our own experience is of 100 normal patients treated with Captopril. I think it was a shame that this otherwise very good drug was introduced at far too high a dose. Initially we gave our patients 450mg daily and all the serious side effects that we have seen, and there were seven in 100, were in the patients with mildly impaired or seriously impaired renal function and getting this higher dose. I think the real message about Captopril is that it is good provided you don’t give it in too large a dose, it’s effective in a low dose, and watch particularly in patients who have renal failure because that’s where the trouble lies.

BERONIADE Yes that was my message.