Merits and demerits of the converting-enzyme inhibitor captopril in antihypertensive treatment

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Chapter 6
Summary, conclusions and look toward the future

6.1 Summary

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure has recently advised that diastolic BP readings of 90 mmHg or more on 2 successive examinations should be regarded as confirmation of hypertension and should be an indication for therapy. Most hypertensive patients can be controlled with dietary regimens alone or in combination with currently available antihypertensive agents. However, the number of patients who are moderate or poor responders to antihypertensive therapy will increase with the rigorous requirements for BP control. There will be, therefore, an increasing need for potent antihypertensive agents. One of these might be the converting-enzyme inhibitor captopril. This antirenin drug is the product of intensive research which was started in the sixties when the influence of the renin system in initiating and sustaining hypertension was increasingly recognized. Preliminary studies with captopril have shown that its antihypertensive properties exceed the results with other currently available therapeutics.

The aim of the present investigation was to study the efficacy of captopril in a large group of hypertensive patients. The studies described are in part a continuation of Prins's studies. However, in this thesis the effects of captopril on blood pressure and the cardiovascular system have especially been described during prolonged treatment. In addition, the vascular and renal responses to the drug were studied in order to gain a better insight into captopril's BP lowering effects. Finally, special attention has been paid to the toxicity of captopril since this might limit clinical applicability (chapter 1).

This study established that captopril is a potent antihypertensive agent. A sustained lowering of BP for periods up to 18 months was observed in a group of 89 patients. These results are the more impressive as this group consisted predominantly of severe or previously uncontrollable cases. The combination of captopril and dietary sodium restriction - with an additional diuretic in 30-40 per cent of all cases - resulted in an adequate BP response

(SDBP < 95 mmHg according to WHO-criteria) in 93 per cent of all patients after one year of treatment. Additional advantages were the rapid occurring BP-response and the absence of reflex tachycardia as well as the absence of postural hypotension. Secondary resistance to the drug developed only in 10 per cent of the patients and was characterized by marked responsiveness to diuretics. Finally, fluid retention did not occur to the same extent as occurring with comparably potent vasodilators.

The therapeutic effect of captopril was objectivated by studying changes in those organs that can be considered target organs for elevated arterial pressure. A significant improvement was observed in fundoscopic, electrocardiographic and roentgenologic parameters of hypertensive damage of arterial vessels and heart. These changes were most dramatic in the first few months of therapy. Therefore, the casual BP readings also most probably indicated adequate BP control (chapter 2).

The way in which captopril lowers BP is incompletely understood. Most investigators agree that blockade of the RAS by CE inhibition plays an important part in the decrease in BP. However, the evidence for this is mainly circumstantial. Our studies disclosed that inhibition of the pressor effects of exogenous A I ran parallel to the decrease in BP. Captopril showed no depressor activity in two different hypertensive states associated with little or no renin. Though there is every reason to conclude from these data that decreased formation of A II plays an important part in the captopril-induced decrease in BP, it appeared that continuous BP control was achieved despite intermittent resumption of normal CE activity. This indicates that the specific effect of captopril administration (inhibition of A II generation) acts together with other mechanisms to control BP throughout the day (chapter 3).

With regard to the renal response to captopril, we observed a decrease in renal vasoconstriction and an increase in renal blood flow. The strong correlation between the percentage change of GFR and of the product of MAP and ERPF during captopril treatment compared with baseline values justifies the conclusion that GFR is maintained by the increase in renal blood flow despite a considerable decrease in BP. Though the mean GFR did not change, the individual patient mostly reacted with either an increase or a decrease in GFR. No differences could be detected in the RVH patients having these different renal responses. However, patients with EH who showed an increase in GFR appeared to be younger than the patients who reacted with a decrease in GFR. The probable explanation for this is that younger patients

have functional, i.e. reversible, changes of the renal vessels, often in combination with an activated RAS. Ageing patients have anatomical changes of the renal vasculature, often in combination with a suppressed RAS. It is therefore no surprise that these categories of patients with EH showed a different renal response to captopril. No conclusive answer can be supplied as to whether changes in renal function contribute to the hypotensive action of the drug (chapter 4).

Before a final conclusion can be drawn as to the place of captopril in antihypertensive treatment, the toxicity of the drug has to be considered. We observed one or more side effects in 30 per cent of our patients. These included rash, sometimes in association with arthralgia and fever, ageusia, proteinuria and anaemia. The drug had to be withdrawn in 8 patients. However, most events were transient and did not prejudice the continued treatment with captopril. The character of side effects, in combination with a parallel increase in auto-antibodies, favours an immunologically mediated pathogenesis. Their high incidence may be a consequence of a special feature of the patients enrolled in this study to develop side effects, the design of the study, or both. With regard to the patients, recent studies have shown an increase of immune reactivity in patients with malignant hypertension. Since many patients with severe, therapy-resistant or malignant hypertension were included in this study, it may well be that the high incidence of side effects is a consequence of our patient selection (chapter 2).

Undoubtedly, the most serious complications were renal (nephrotic syndrome) and haematological (agranulocytosis). With regard to the former, we reviewed all available data on development of proteinuria during captopril therapy. It appeared that proteinuria occurred in a frequency of 7.4 % in a single center study in New York whereas we found in our own study 4.5 %. Membranous glomerulopathy at an early stage was unvariably established in all patients who underwent a renal biopsy having captopril-associated proteinuria. However, proteinuria seems to be an unreliable marker for the presence of MGP since urinary protein loss may be transient even without discontinuing the drug. The way in which captopril induces MGP is unknown. It is possible that auto-antibodies, which result from immunodysregulation, play a part in the pathogenesis. As for the clinical impact of the histological lesions, it is as yet unknown whether MGP will progress to renal function loss by the development of a thickened GBM or, alternatively, may heal completely.

Our studies indicated that patchy immunoglobulin deposition and atypical, small, very dense deposits in EM are found in most patients with hypertension before captopril treatment. The atypical particles were also seen in biopsies of a control group (transplant biopsies). No differences could be established between pre- and post-captopril biopsies. These observations are conclusive evidence that captopril is not associated with the development of these ultrastructural abnormalities (chapter 5).

6.2 Conclusion

Captopril is highly effective in lowering blood pressure, especially in combination with sodium restriction. The main mechanism of captopril's BP lowering-action is inhibition of the RAS. The drug increases renal blood flow and decreases renal vasoconstriction while GFR is maintained despite a considerable fall of BP. Though captopril is an antihypertensive agent with undoubted potency, its associated side effects, some of them serious, limit unlimited clinical applicability.

Our present knowledge suggests that captopril should be reserved for the treatment of hypertension which is untreatable by other currently available drugs.

6.3 Look toward the future

So far, no studies have come to hand that deal with optimum dosaging of captopril. Future studies should focus on this important issue and should pay attention to the relative significance of dietary sodium restriction and diuretics in obtaining the maximum effect of captopril in the lowest dosages. The question as to whether lower dosages than currently used will diminish the frequency of side effects, may be answered in these studies.

The remarkable efficacy of captopril (i.e. the principle of converting-enzyme inhibition) has stimulated many pharmaceutical industries to develop orally active CE inhibitors. Since it was thought that the SH group might be responsible for the side effects of captopril, the design of this research has been focussed on the development of a CE inhibitor without a mercapto-group[230]. One must be aware, however, that no conclusive evidence is available at the present time that it is only this mercapto-group which is involved in the range of captopril-associated side effects. It should not be forgotten that the principle of CE inhibition per se is by no means beyond suspicion of playing a part in the pathogenesis of side effects.