Special Report

Review of the Overall Experience of Captopril in Hypertension

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• **The pharmacologic profile of the angiotensin–converting enzyme inhibitor, captopril, is described. After reviewing the total clinical experience of captopril from the world literature and manufacturer's files, a small subgroup of clinically complex patients at particular risk of side effects and in whom the drug must be used with caution is characterized. Evidence is available that demonstrates that lower doses (150 mg/day or less, with modest doses of diuretic agents) are effective in both short- and long-term therapy, while the incidence of side effects is substantially reduced. With this background information, the benefit-risk ratio is substantially improved and the use of captopril as a primary agent in the management of hypertension may be considered.**

(*Arch Intern Med* 1984;144:1441-1444)

Antihypertensive therapy usually has taken the form of stepped-care regimens, commonly beginning with a small dose of a diuretic agent, usually a thiazide congener, although the use of β-blocking drugs as primary therapy is increasing, especially in Europe. The dose of the initial agent is either increased or one or more other drugs are added as required to achieve control of blood pressure. This approach permits interaction of various agents, which make possible lower doses of individual drugs, thereby minimizing untoward effects. Second-step therapy includes the β-blockers; centrally acting agents, eg, methyldopa and clonidine hydrochloride; the α-blockers, eg, prazosin hydrochloride and reserpine; and most recently, the orally active angiotensin-converting enzyme inhibitor, captopril.

Most antihypertensive drugs effectively lower arterial pressure but often have unwanted side effects that may limit patient acceptance and adherence; some have specific contraindications that preclude their use in certain patients.

Although captopril is efficacious in most forms of hypertension, its use largely has been limited because of safety considerations to patients with severe, treatment-resistant hypertension. Recent reports of studies using lower doses, usually in combination with a diuretic, suggest, however, that while antihypertensive efficacy is maintained, the safety profile of captopril could be reappraised. The purpose of this article is to review the available data and published reports on the safety and efficacy of captopril therapy in light of the new findings.

DATA ANALYSIS

The total data base of clinical studies conducted by the manufacturer (E. R. Squibb & Sons Inc, Princeton, NJ) was made available to us for determination of the safety and efficacy of captopril therapy. This analysis also included a review of the recent world literature concerning those clinical studies in which captopril had been administered to patients with milder forms of hypertension using doses considerably less than those employed in the initial efficacy trials.[1-5] This broader clinical experience permitted evaluation of the relationship of drug dosage and renal functional status.

Neutropenia was considered captopril-associated if the case history met all of the following criteria:

1. Two consecutive absolute neutrophil counts less than 1,000/cu mm or a single neutrophil count less than 1,000/cu mm with either evidence of decreased myelopoiesis on bone marrow examination or a downward trend of the WBC count during the preceding days or weeks.
2. Failure of the depressed absolute neutrophil count to rise during continued captopril therapy.
3. Absence of preexisting chronic leukopenia.
4. In patients receiving concomitant cytotoxic chemotherapy, resolution of neutropenia on discontinuation of captopril therapy alone or, if both drugs were discontinued, recurrence of neutropenia when captopril alone was readministered.

The criteria for possible captopril-associated proteinuria for the hypertensive population studied are that two of any three consecutive monthly urinary protein determinations during therapy be (1) greater than or equal to 1.0 g/24 hr (or greater than or equal to a dipstick reading of greater than or equal to 3+) for patients whose pretreatment dipstick reading was mild (≤1+), or (2) at least twice the baseline value for patients whose pretreatment dipstick reading was moderate (≥2+) (or who were excreting ≥1.0 g/24 hr pretreatment).

DOSAGE

The early clinical study protocols provided for captopril daily dosages of 75 mg (in three divided doses) that were increased at weekly intervals to 150, 300, and 450 mg/day (also in three divided doses). These doses were employed before a diuretic or other antihypertensive agent (usually a β-blocker) was introduced. Since the maximum sustained antihypertensive effect of captopril may not be achieved for two to three weeks, excessive doses of the drug due to rapid titration were frequently employed in these early studies. Later studies demonstrated that when diuretics were introduced before these maximum permitted doses of captopril were reached, a marked synergistic antihypertensive effect could be expected.[1,2,5] Therefore, higher doses of captopril (300 mg/day and 450 mg/day) were probably only rarely required for adequate pressure control.

Because captopril is excreted completely by renal mecha-

Accepted for publication Nov 16, 1983.

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nisms, lower doses should be administered to patients with impaired renal function. Such adjustments were made rarely during the early clinical trials; and since 26% of all patients in these studies had renal impairment (Squibb Institute for Medical Research, unpublished data on file), it is not surprising that the frequency of side effects was relatively, and at times unacceptably, high.

RASH AND DYSGEUSIA

Rash and dysgeusia (alteration of taste), both self-limiting, appeared usually during the first three months of therapy with frequencies of 10% and 7%, respectively, with daily doses of 450 mg or more (Squibb Institute for Medical Research, unpublished data on file). In many instances rash and dysgeusia resolved, despite continuation of the drug, sometimes without dose reduction. This was confirmed by the discontinuation rates of 1.4% for rash and 0.5% for dysgeusia when daily doses of 150 mg were administered to patients with normal renal function (serum creatinine level, ≤1.5 mg/dL) (Figs 1 and 2) (Squibb Institute for Medical Research, unpublished data on file).

In a recent and ongoing multicenter surveillance study 66% of the 5,000 patients enrolled received captopril in daily doses of 150 mg or less. The frequency of rash and dysgeusia was virtually halved to 5% and 4%, respectively. The 638 patients completing one year in this study had an average entry arterial pressure of 181/111 mm Hg (while receiving an average of 3.1 antihypertensive drugs) that was reduced to 151/92 and 149/89 mm Hg after three and 12 months, respectively. Eighty-seven percent of these patients required only captopril with a thiazide diuretic (Squibb Institute for Medical Research, unpublished data on file).

NEUTROPENIA

Neutropenia is the most important, although least frequent, side effect associated with captopril. An analysis of 5,632 patients demonstrated that neutropenia occurred predominantly in definable subgroups of patients[6] that could be related to coexistent complicating diseases. As of May 1983, 63 cases of captopril-associated neutropenia had been reported worldwide; 14 occurred in clinical studies. As has been noted with other drugs, in most instances captopril-induced neutropenia occurred within the first 12 weeks of therapy; and no clear dose relationship could be discerned. Neutropenia was the only cytopenia reported in 52 of the 63 cases, and the neutrophil counts usually rose promptly (median, ten days) when captopril therapy was discontinued. In 11 of the 63 cases, neutropenia was accompanied by thrombocytopenia, and bone marrow samples in these patients were panhypoplastic. In contrast to patients with neutropenia alone, this latter subset of patients had a high morbidity and mortality.

Development of neutropenia was strongly influenced by coexistent renal insufficiency and collagen-vascular diseases (eg, scleroderma and systemic lupus erythematosus [SLE]); and two thirds of the entire group of 63 patients with captopril-associated neutropenia had significant azotemia, a collagen-vascular disease, or both. Cooper,[6] in his review of the 5,632 patients, found 4,544 patients with normal renal function and without collagen-vascular disease. Of these 4,544 patients, there was only one (0.02%) with neutropenia (Table). In contrast, five of 997 (0.5%) other hypertensive patients with significantly impaired renal function (serum creatinine level, >2.0 mg/dL) had neutropenia. Finally, of the remaining 111 patients with both azotemia and a collagen-vascular disease, eight (7.2%) had neutropenia. Thus, although neutropenia is a potentially serious side effect, it seems to occur primarily in well-defined risk groups, detectable with serially obtained WBC counts during the first 12 weeks of therapy.

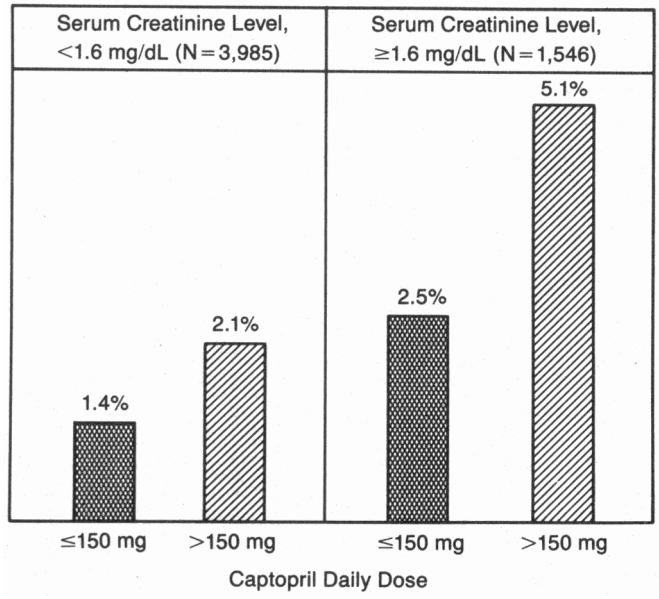

Fig 1.—Frequency of discontinuation of captopril therapy because of rash.

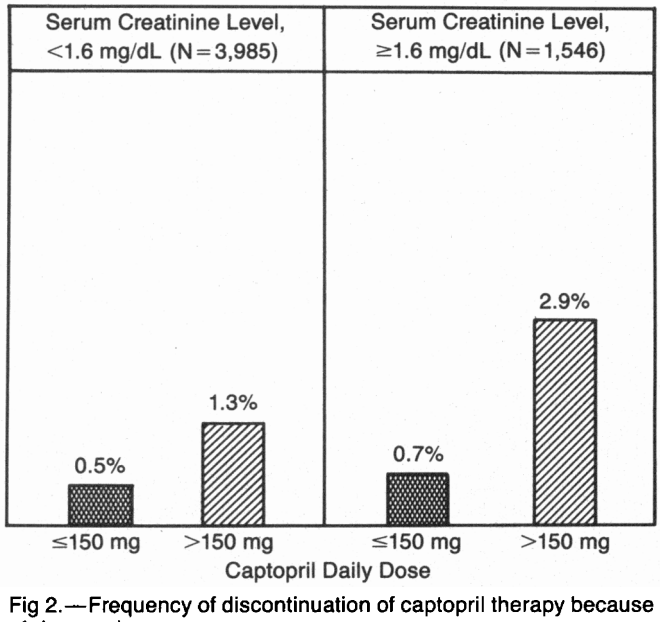

Fig 2.—Frequency of discontinuation of captopril therapy because of dysgeusia.

In the surveillance study, in which the captopril dose was 150 mg/day or less in the majority of patients, there was no incident of neutropenia in 1,720 patients with normal renal function on entry (serum creatinine level, ≤1.5 mg/dL) who completed at least three months of therapy. Two cases of neutropenia occurred, however, among the 604 patients with impaired renal function. Both of the patients had serum creatinine concentrations greater than 2.0 mg/dL, and they also had collagen-vascular disease (SLE in one and scleroderma in the other). Prompt recovery occurred in both patients when captopril therapy was discontinued (Squibb Institute for Medical Research, unpublished data on file).

Frequency of Captopril-Associated Neutropenia				
	Serum Creatinine Level, mg/dL			
	<2.0		≥2.0	
	No Collagen Vascular Disease	With Collagen Vascular Disease	No Collagen Vascular Disease	With Collagen Vascular Disease
Total No. of patients	4,544	61	997	111
No. of patients with neutropenia	1	0	5	8
Frequency of neutropenia, %	0.02	0	0.5	7.2

PROTEINURIA

Proteinuria, sometimes sufficient to produce the nephrotic syndrome, usually occurred between the third and ninth months of therapy and was reported in 70 (1.2%) of the 5,769 patients. This required discontinuation of captopril therapy in 37 cases. Of the remaining 33 patients who continued receiving captopril therapy, the proteinuria had completely disappeared in 18 patients at the time of this article. In these studies, captopril was frequently administered to patients with altered renal function; and the Captopril Collaborative Study Group[7] suggested that in some patients the proteinuria may have reflected preexisting renal parenchymal disease.

Seventy-five percent of the patients having proteinuria were receiving daily doses in excess of 150 mg, and 71% had had a history of preexisting renal disease. Groel et al[8] reported that proteinuria occurred in 36 (3.5%) of the 1,016 patients with preexisting renal disease who received daily doses of more than 150 mg. In contrast, among 2,126 patients without a history of renal disease who received doses of 150 mg/day or less there were only four cases, an incidence of 0.2% ($P<.0001$). There was no deterioration of renal function in patients with normal serum creatinine concentrations on entry in whom proteinuria subsequently developed. Some with renal dysfunction before treatment had further deterioration in function (based on serum creatinine determinations) with therapy, although this may have reflected progression of the underlying renal disease. Therefore, as with neutropenia, if a relationship of proteinuria with captopril exists, it seems to occur in a well-defined population at risk (Fig 3).

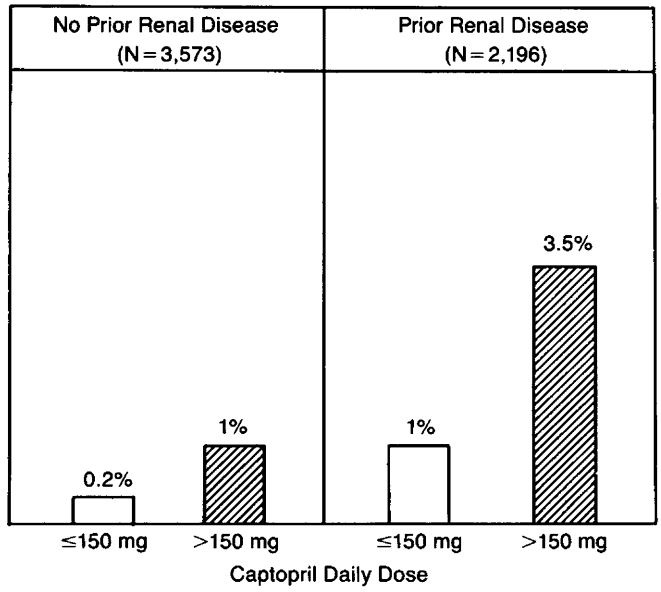

Fig 3.—Frequency of proteinuria in formal clinical trials.

FIRST-DOSE EFFECT

An exaggerated fall in arterial pressure may occur after the initial dose of captopril, particularly in patients with high levels of circulating angiotensin II (eg, renovascular hypertension),[9] patients with hypertension or congestive heart failure who had been treated aggressively with diuretics,[10] and in patients undergoing renal dialysis therapy.[11] Thus, in these clinical situations, the hypotension should not be unexpected.[12] Few of the patients exhibiting hypotension, however, were symptomatic.[13]

Cremer[14] found in a double-blind study of 350 mild to moderately severe hypertensive patients, some with and some without diuretic pretreatment, that only 8.6% had mild, transient symptoms of hypotension following the initial dose of captopril (mild dizziness or lightheadedness); no patient required medical intervention. Experimental animal studies demonstrated that, following the initial dose of captopril, a redistribution of regional blood flow occurred that coincided with the fall in pressure, resulting in an increase of cerebral perfusion.[15]

RENAL EFFECTS

In patients with bilateral renal artery stenosis or stenosis of a renal artery to a solitary kidney, renal function may be compromised as a result of reduced renal perfusion pressure and the captopril-induced inhibition of intrarenal angiotensin II generation.[16-18] In some instances, renal autoregulatory mechanisms may adapt the renal circulation to the reduced perfusion pressure, resulting in restored renal function; whereas in others normal renal function was restored when the drug was either discontinued or administered at reduced doses.[9]

LONG-TERM SAFETY AND EFFICACY

Groel et al[8] reported that in 7,103 patients treated with captopril (representing more than 5,000 patient-years), the antihypertensive effect was maintained over the long term without evidence of tolerance. In early studies, using high doses of captopril (mean, >300 mg/day), 1,808 patients were treated for 12 months, with a cumulative discontinuation rate (life-table method) due to adverse reactions of 8.5%. The majority of these discontinuations occurred during the first three months of therapy. During the 12-month period, the cumulative dropout rate due to treatment failure was 4.7%. In 531 patients treated for two years, 153 of whom were treated for three years, and a small number for four years, control of pressure was maintained without evidence of tolerance; the four-year cumulative frequency of discontinuation due to side effects was 11.6%.

In the surveillance study, 638 patients completed 12 months of therapy. Adequate control of pressure was maintained with lower doses of captopril; the one-year cumulative discontinuation rate due to adverse reactions was reduced significantly to 5.5%, while that due to treatment failure was essentially the same as in earlier studies (4.4%) (Squibb Institute for Medical Research, unpublished data on file).

The Veterans Administration Cooperative Study Group[1] concluded that captopril was safe and effective when given

two or three times daily in low doses to patients with mild hypertension. Of 384 patients completing 14 weeks of therapy, only 15 patients (3.9%) required discontinuance of the drug because of side effects. In the long-term part of the study, an additional seven (4.1%) of 171 patients treated for periods of 12 months had captopril therapy discontinued because of side effects; none was life threatening (Squibb Institute for Medical Research, unpublished data on file).

Biochemical measurements were monitored regularly during long-term captopril therapy and were essentially unchanged, except for those indices produced by inhibition of the angiotensin-converting enzyme. Serum potassium concentration tended to increase slightly with captopril monotherapy, balancing the tendency to hypokalemia induced by concomitant diuretic therapy (Squibb Institute for Medical Research, unpublished data on file).[1] Weinberger[2] reported that the changes in serum glucose, cholesterol, and uric acid concentrations frequently associated with diuretics were minimized with added captopril. Finally, captopril did not possess CNS-depressant effects, nor did it affect sexual function.

Karlberg et al[19] described 74 hypertensive patients who were treated with captopril and hydrochlorothiazide and followed up during periods of four years; a cohort of 42 of these patients was treated for three years. During this period, the average dose of captopril was reduced slightly from 217 to 199 mg/day. Only one patient required an additional drug (propranolol hydrochloride) to control pressure. Of these 42 patients, pressure was reduced from 173/110 to 142/90 mm Hg after three years, and heart rate was reduced insignificantly from 75 to 70 beats per minute. Of the 74 patients, one patient discontinued captopril therapy due to an adverse reaction (stomatitis) and proteinuria developed in another patient (1.8 g/24 hr) after four months and resolved with dose reduction. During therapy no changes were observed in regular determinations of serum sodium, potassium, alkaline phosphatase, aspartate aminotransferase, creatinine, glucose, cholesterol, or triglyceride concentration.

COMMENT

While diuretics still remain the primary therapy for hypertension, increasing numbers of physicians now consider selecting agents that may be more specific for a particular patient. β-Blockers may be indicated for patients with cardiac arrhythmias or angina pectoris, or in young patients with a hyperdynamic circulation and cardiac awareness.[20] Angiotensin-converting enzyme inhibition, while effective in most forms of hypertension, is especially indicated for patients with high renin hypertension, or hypertension complicated by diabetes mellitus or congestive heart failure.[1,9,10,13]

Most antihypertensive drugs effectively lower arterial pressure, but each may produce unwanted side effects that may limit patient acceptance and adherence. The safety of diuretics administered in relatively large doses for long periods recently has been questioned.[21,22] β-Blockers may have a greater frequency of side effects if specific patients who are predisposed to them are not excluded from treatment[20]; and sympatholytic and peripheral vasodilating agents also have side effects that could limit their use.[23-25]

Safety and efficacy should be considered in selecting antihypertensive therapy. Safety considerations must include both objective manifestations of toxic effects and subjective experiences that may affect patient acceptance. Large-scale studies have demonstrated that the majority of uncomplicated hypertensive patients may be treated effectively with modest doses of captopril (150 mg/day or less, with or without a diuretic), with little risk of toxic effects. These studies have also demonstrated a small, but definable, subgroup of patients in whom there may be greater risk of more serious side effects. The majority of the latter patients were severely ill with additional diseases, and many of these patients were refractory to standard antihypertensive therapy. While captopril therapy will often lower their pressure, WBC counts and urinary protein excretion should be monitored closely, especially during the first three months of therapy.

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