BRIEF REPORT

HYPERTENSIVE CRISIS IN SYSTEMIC SCLEROSIS: TREATMENT WITH THE NEW ORAL ANGIOTENSIN CONVERTING ENZYME INHIBITOR MK 421 (ENALAPRIL) IN CAPTOPRIL-INTOLERANT PATIENTS

C. DOUGLAS SMITH, RONALD D. SMITH, and JOSEPH H. KORN

Renal disease is a major cause of mortality in patients with systemic sclerosis. In the past, the syndrome of malignant hypertension with renal failure was almost uniformly fatal within months (1). The use of dialysis, nephrectomy, and transplantation resulted in some apparent improvement in survival, but the complication rate has been high (2). Since 1978, a number of reports have appeared suggesting that aggressive medical therapy of hypertension could lead to stabilization, if not reversal, of the syndrome. In 1979 the first report of successful use of the oral angiotension converting enzyme (ACE) inhibitor, captopril, appeared. Since that time, experience with about 20 patients has been reported with generally favorable results (3–5). This has led to the suggestion that captopril may be the drug of choice for systemic sclerosis patients with this complication.

We recently treated 2 patients with malignant hypertension and renal involvement complicating systemic sclerosis, who responded well to captopril. Their course, however, was complicated by persistent side effects which necessitated withdrawal of the drug. Both patients were then treated with the investigational ACE inhibitor, MK 421 (Enalapril), and responded with control of their blood pressure, improvement in renal function, and disappearance of side effects.

Patient 1. A 58-year-old woman was seen in April 1982 with a 10-year history of Raynaud's phenomenon and a 4-month history of seronegative symmetric polyarthritis with morning stiffness. She had a long history of mild hypertension which had been treated with diuretics and reserpine. Over the next 6 months, she developed proximal scleroderma (face, chest, legs), telangiectasia, and symptoms of reflux esophagitis. Her blood pressure and renal function remained normal. In November 1982 she complained of increasing fatigue.

Examination showed a blood pressure of 190/110, arteriolar narrowing, and a prominent apical S4. Laboratory investigations revealed the following values: hemoglobin 12.4 gm/dl with a normal smear, blood urea nitrogen (BUN) 31 mg/dl, serum creatinine 2.1 mg/dl, urinalysis 1+ protein; a chest radiograph revealed mild cardiomegaly. She was started initially on captopril, 25 mg 4 times daily, which was increased over the next 2 weeks to 75 mg 4 times a day with good control of her blood pressure. During this period, her creatinine level rose to a peak of 4.7 and then began to decline (Figure 1).

Four weeks after institution of captopril therapy, she developed a diffuse pruritic maculopapular rash, as well as severe dysgeusia with a persistent salty-metallic taste. With reduction of her captopril dosage, the rash disappeared, but the marked taste disturbance and resulting poor food intake persisted.

From the Division of Rheumatic Diseases, The University of Connecticut School of Medicine, Farmington, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania, and The Veterans Administration Medical Center, Newington, Connecticut.

Supported in part by an NIH Multipurpose Arthritis Center grant, an Arthritis Foundation Clinical Research Center grant, and a grant from the Connecticut Chapter of the Arthritis Foundation. Dr. C. D. Smith is a Fellow of the Canadian Arthritis Society.

C. Douglas Smith, MD: Division of Rheumatic Diseases, University of Connecticut School of Medicine; Ronald D. Smith, MD: Merck Sharp and Dohme Research Laboratories; Joseph H. Korn, MD: VA Medical Center and The University of Connecticut School of Medicine.

Address reprint requests to Joseph H. Korn, MD, Division of Rheumatic Diseases, VA Medical Center/151, Newington, CT 06111.

Submitted for publication November 21, 1983; accepted in revised form February 8, 1984.

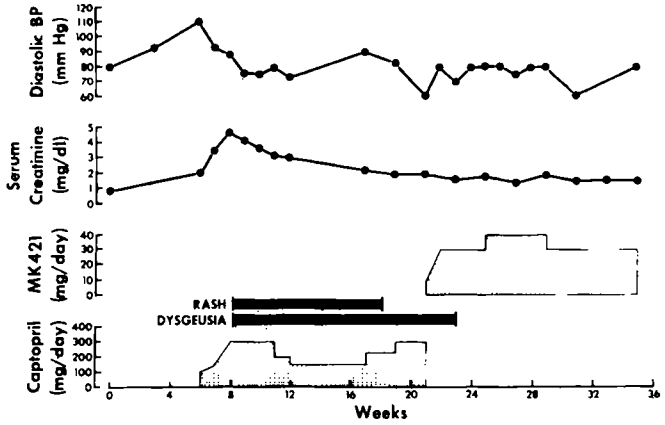

Figure 1. Captopril and MK 421 treatment profile of patient 1, a 58-year-old woman with scleroderma-related hypertensive renal crisis.

After informed consent was obtained, captopril was discontinued and MK 421, 5 mg twice a day, was begun. Over the next month, the dosage was increased to 40 mg daily with excellent control of her blood pressure, continued improvement in her renal function, and resolution of the dysgeusia. Five months after the onset of malignant hypertension and 4 months after beginning MK 421, she was taking MK 421 30 mg/day, had blood pressure of 120–180/70–80, BUN 29 mg/dl, and creatinine 1.5 mg/dl.

Patient 2. A 39-year-old man developed Raynaud's phenomenon in February 1980, followed by symmetric seropositive polyarthritis and morning stiffness. In January 1981 he had an episode of pericarditis and myocarditis which resolved without specific therapy. Between February and April 1981 he developed rapidly progressive, diffuse scleroderma as well as general fatigue and symptoms of reflux esophagitis. He was treated with low doses of prednisone without improvement. Blood pressure, renal function, and pulmonary function remained normal.

In September 1982 he complained of 3 weeks of marked fatigue, a bifrontal headache, and dyspnea on minimal exertion. Examination was remarkable for a blood pressure of 210/140, fundi showing arteriolar narrowing only, dry bibasilar crepitations, and a loud apical S4. Laboratory investigations revealed: hemoglobin 12.5 gm/dl with normal red cell morphology; white blood cells 6,400/mm, platelets 114,000/mm, BUN 45 mg/dl; creatinine 3.8 mg/dl; urinalysis 2+ protein, 4–6 red blood cells/high-power field, and occasional granular casts; chest radiographs showed cardiomegaly with increased interstitial marking at the bases.

Treatment with captopril was initiated and the dosage was increased over the next 4 days to 100 mg 4 times a day. He was also given nitroprusside and intermittent dosages of furosemide. His blood pressure was reduced to 120/60, the platelet count returned to normal, but his renal function deteriorated initially with urea nitrogen levels rising to 94 mg/dl and creatinine rising to 6.2 mg/dl. With his blood pressure under control, the captopril dosage was reduced to 50 mg twice a day and his renal function improved (BUN 46 mg/dl) and his creatinine stabilized (4.2 mg/dl). At this time, 4 weeks after captopril therapy was initiated, he developed a diffuse pruritic rash with desquamation. Captopril was discontinued and he was started on propanolol and prazosin. Within 48 hours his blood pressure had risen to 160/100 and his renal function began deteriorating. After propanolol, prazosin, and nifedipine failed to control his blood pressure, captopril was restarted at 25 mg 4 times daily. Two weeks after the captopril was resumed, blood pressure control was still suboptimal, renal function deteriorated, and the rash persisted. Eight weeks after the onset of malignant hypertension and 2 weeks after captopril was restarted, his blood pressure was 166/100 and his serum creatinine level was 9.1.

After informed consent was obtained, captopril was discontinued and the patient was started on MK 421, 2.5 mg twice daily orally. The dosage was increased over 1 week to 10 mg 3 times a day with resultant excellent control of his blood pressure (diastolic 60–80 mm Hg). Two weeks later, his rash had disappeared but his creatinine level had risen to 12.8 mg/dl. Hemodialysis was started and was continued for 8 weeks. Control of his blood pressure remained excellent and the dosage of MK 421 was reduced to 5 mg daily. His renal function improved and the dialysis was discontinued. Nine months after the onset of malignant hypertension and 4 months after discontinuing dialysis, he was doing well on a regimen of MK 421, 5 mg daily, with a blood pressure of 110/70 and a serum creatinine level of 4.0 mg/dl. His renal function is continuing to improve and there has been no recurrence of the rash. Over the entire period since the onset of renal failure, he has noted considerable skin softening.

Discussion. Both patients reported here developed rapidly-progressive hypertension and renal insufficiency as a manifestation of systemic sclerosis. Both responded to captopril with control of blood pressure and stabilization of renal function. Management was complicated by the development of intolerable side

effects to captopril. In the first patient, the rash disappeared with continued therapy but the severe taste disturbance persisted. In the second patient, a significant rash with severe pruritis persisted and attempts to lower the dose of captopril resulted in loss of blood pressure control and worsening renal insufficiency. With the use of MK 421, good blood pressure control was achieved and significant improvement of renal function followed. Side effects cleared and did not recur.

Side effects of captopril therapy have included rashes in 10–14% and taste disturbances in approximately 6% of patients treated. These represent the most common side effects and are usually self-limited even with continued therapy. More serious side effects have included proteinuria with a membranous glomerulopathy in 1.2% and neutropenia in 0.3% of patients, with a few cases of fatal agranulocytosis (6,7). The similarities in the spectrum of toxicity between captopril and D-penicillamine suggest that the presence of a sulfhydryl group on both compounds may be responsible (5,6). Alternatively, potentiation of cutaneous kinins has been postulated as a mechanism for captopril-induced skin rashes (8).

Molecular manipulation has led to the development of a more potent investigational ACE inhibitor, MK 421. It was believed that because MK 421 lacks a sulfhydryl group, it might result in fewer adverse effects (9). Gavras and Gavras have recently reported lack of side effects to MK 421 in 4 patients who developed cutaneous reactions to captopril (10). The successful substitution of MK 421 in our captopril-intolerant patients would suggest that the common side effects of rash and dysgeusia may, indeed, be associated with the presence of a sulfhydryl group. Similarly, since MK 421 is a more potent inhibitor of kininase II than is captopril, it seems unlikely that rashes can be explained on the basis of cutaneous kinin potentiation (8).

These cases add further evidence that early and aggressive therapy, particularly with ACE inhibitors, can produce stabilization if not improvement in renal function in patients with this previously lethal complication of systemic sclerosis. In patients intolerant of captopril, the use of another ACE inhibitor such as MK 421 should be considered.

Acknowledgment. We wish to acknowledge the kind assistance of Dr. Phillip Rodel in supplying MK 421.

REFERENCES

1. Medsger TA, Masi AT: Survival with scleroderma. II. A life-table analysis of clinical and demographic factors in 358 male U.S. veteran patients. J Chronic Dis 26:647–660, 1973
2. LeRoy EC, Fleischman RM: The management of renal scleroderma: experience with dialysis, nephrectomy and transplantation. Am J Med 64:974–978, 1978
3. Lopez-Ovegero JA, Saal SD, D'Angelo WA, Cheigh JS, Stenzel KH, Laragh JH: Reversal of vascular and renal crises of scleroderma by oral angiotensin-converting-enzyme blockade. N Engl J Med 300:1417–1419, 1979
4. Zawada ET, Clements PJ, Furst DA, Bloomer HA, Paulus HE, Maxwell MH: Clinical course of patients with scleroderma renal crisis treated with captopril. Nephron 27:74–78, 1981
5. Whitman HH III, Case DB, Laragh JH, Christian CL, Botstein G, Maricq H, LeRoy EC: Variable response to oral angiotensin-converting-enzyme blockage in hypertensive scleroderma patients. Arthritis Rheum 25:241–248, 1982
6. Captopril: benefits and risks in severe hypertension (editorial). Lancet 1:129–130, 1980
7. Vidt DG, Bravo EL, Fouad FM: Captopril. N Engl J Med 306:214–219, 1982
8. Wilkin JK, Hammond JJ, Kirkendall WM: The captopril-induced eruption: a possible mechanism: cutaneous kinin potentiation. Arch Dermatol 116:902–905, 1980
9. Gavras H, Waeber B, Gavras I, Biollaz J, Brunner HR, Davies RP: Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421." Lancet 2:543–547, 1981
10. Gavras I, Gavras H: Captopril and Enalapril (letter). Ann Intern Med 98:556, 1983