Captopril-Induced Creatine Kinase Elevations: A Possible Role of the Sulfhydryl Group

To the Editor:

Since captopril, the first orally active angiotensin converting enzyme inhibitor, was introduced into clinical medicine, this new approach to blocking the formation of angiotensin II and lowering the blood pressure, appears to be tolerated well in most hypertensive patients.1 However, during a randomized trial comparing the antihypertensive efficacy of captopril, 25 mg b.i.d., with captopril, 25 mg t.i.d., we found elevated creatine kinase (CK; EC 2.7.3.2) levels in several patients. In the present study, therefore, CK levels in 44 patients with mild to moderate hypertension (24 men and 20 women; average age, 53.5 ± 2.0 [S.E.] years) treated with captopril were reviewed retrospectively. Thirty of these patients were treated with captopril alone, while 14 were treated with captopril in addition to other hypotensive agents: diuretics in eight, β-blockers (atenolol) in two, diuretics with β-blockade in three (atenolol in one, propranolol in two) and nifedipine in one. The duration of treatment ranged from 1 to 26 months. The average captopril dosage was 60.7 mg/day and ranged from 25 to 75 mg/day. (Unless otherwise specified, all data are expressed as means ± SE.)

Blood pressure declined significantly from 167 ± 2.1/95 ± 1.7 (n = 44) to 156 ± 2.1/91.3 ± 1.5 (n = 44), 149 ± 2.3/91 ± 1.8 (n = 31), and 144.9 ± 4.5/87.4 ± 3.6 mm Hg (n = 15) after 4, 16, and 32 weeks, respectively, of captopril administration.

Before treatment with captopril, three of the 44 patients had a CK value that exceeded our hospital's normal range (11–136 IU/L). In the remaining 41 patients, CK activities were determined 47 times before and 161 times after treatment. Captopril administration significantly elevated CK activities from 71.9 ± 4.3 to 84.7 ± 3.3 IU/L (p < 0.05). When reanalyzed according to the dosage of captopril, the average CK levels were 82.2 ± 3.7 (n = 56 determinations, NS) at 25 to 37.5 mg/day and 86.0 ± 4.6 IU/L (n = 105 determinations, p < 0.05) at 50 to 75 mg/day. As a result, 20 CK determinations in six patients exceeded their pretreatment mean + 2 SD of 131.5 IU/L. The time course of CK values in five of these six hypertensive patients is illustrated in Figure 1. On the other hand, in one (Patient 7 in Figure 1) of three patients with a high initial CK level, combined treatment with captopril, 75 mg/day, and indapamide, 1 mg/day, resulted in a further, progressive, 3-month rise in CK (from 143 to 179 to 300 to 334 IU/L) followed by normalization of CK activity 1 month after drug administration was stopped. One month later, captopril challenge at 50 mg/day again increased CK activity to 224 IU/L. Another patient with initially high CK levels also exhibited a progressive increase of CK (from 147 to 185 and 184 IU/L after 3 and 3.5 months, respectively, of captopril 37.5 mg/day). In the third patient with high pretreatment levels (438 IU/L), CK activity remained high (395 IU/L) 1 month after treatment with captopril, 50 mg/day.

Normal CK levels at our hospital averaged 73 ± 31.4 (SD) IU/L in 206 healthy subjects aged 14 to 86 years old. Ten out of 206 subjects demonstrated higher CK values (i.e., exceeding mean values + 2 SD). Before captopril administration, the incidence of higher CK values was similar in hypertensive subjects (3 of 44) and controls (10 of 206). However, the number of hypertensive patients showing CK elevations during captopril treatment, while comparable to that noted during β-blockade,2 was significantly different from that seen in controls, even after excluding Patient 9 (8 of 43 vs 10 of 206; χ² = 10.03, p < 0.005).

To check the origin of the CK, isozymes of CK were evaluated using 19 samples from subjects with elevated CK levels. Neither the MB nor the BB isozyme fluctuated in any sample, except in two samples from Patient 9, which contained 3.4 and 6.1% CK-MB, respectively, before and after captopril administration. Serum lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT) activities were also analyzed. Excluding values in eight patients with chronic hepatic damage, LDH, SGOT, and SGPT levels (21.0 ± 6.1, 24.9 ± 1.3, and 30.1 ± 1.7 mU/ml, respectively) did not change after captopril administration (n = 138) as compared with pretreatment controls (199.5 ± 5.4, 226 ± 1.0, and 25.5 ± 1.8 mU/ml, respectively; n = 42). Even in the patients with some hepatic injury, captopril treatment did not result in any further rise in LDH, SGOT, and SGPT activities. In addition, these enzyme activities did not fluctuate in the patients demonstrating high CK values after oral captopril intake.

Although 0.6% and 0.01% of the patients treated with captopril demonstrated myalgia or muscle cramps in the general use study3 and the Japanese Phase IV study,4 respectively, none of the patients complained of myalgia or muscle cramps in the present study. Taken together with the lack of a rise in SGOT and LDH, these results militate against the possibility that captopril increases the release of CK from skeletal muscles or damages skeletal muscles.

CK is one of the enzymes that need a sulfhydryl group for full activation,5 since CK contains at least one cysteine residue per subunit near the catalytic
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In fact, commercial kits for CK determination contain one or all of the sulfhydryl reagents 1,4-dithiothreitol, N-acetyl-L-cysteine, and glutathione to activate the enzyme. The kit used in our hospital (Calbiochem-Behring, San Diego, CA, USA) contains N-acetyl-L-cysteine and 1,4-dithiothreitol at final concentrations of 10.5 and 8.6 mM, respectively, according to the method of Rosalki. Thus, we investigated the possibility that the sulfhydryl group in the captopril molecule might result in in vitro activation of CK in the reaction mixture during analysis. Although further addition of 1 mM 1,4-dithiothreitol to the serum in vitro resulted in a rise in CK activity to 214 ± 16.9 from 98 ± 9.7 IU/L (n = 7, p<0.01) after 3 hours, a 24-hour incubation of the serum with captopril even at 1 or 20 mM 1,4-dithiothreitol did not increase CK levels (92 ± 9.2 and 102 ± 9.9 IU/L, respectively). The added dose of captopril used in the present study is far greater than the maximum plasma concentration, which was reported to be about 4 μM 2 hours after a 25-mg oral dose of captopril. Thus, it seems unlikely that captopril could induce a false increase in the assay system.

Finally, normotensive volunteers aged 28 to 38 years old were given captopril, 125 mg over 20 hours, 50 mg at Time 0 and 25 mg 8, 16, and 20 hours later, which decreased (but not significantly) blood pressure from 123.6 ± 4.3/82.5 ± 3.5 to 116.9 ± 2.6/72.8 ± 2.1 mm Hg after 24 hours. The results of CK serial determination are shown in Figure 2. Two of nine subjects showed a continuous increase in CK activities from 93 to 120 and from 250 to 645 IU/L after 24 hours. A transient CK increase was observed in the other two subjects (from 118 to 142 IU/L at 2 hours and from 119 to 130 IU/L at 5 hours). The results revealed

**FIGURE 1.** Time course of creatine kinase (CK) activities in individual patients treated with captopril alone or with captopril and indapamide. Months are represented by roman numerals.

**FIGURE 2.** Time course of creatine kinase (CK) activities in normotensive volunteers before and after administration of captopril, 50 mg at Time 0 and 25 mg 8, 16, and 20 hours later.
a very prompt increase of CK within 24 hours in some subjects, indicating a rather rapid interaction of CK with captopril. Sulphydryl blocking agents, such as iodoacetamide or N-ethylmaleimide, usually lead to loss of the enzymatic activity of CK through a configurational change. If some sulphydryl blocking agents reactive with captopril in vivo exist, then captopril may protect the sulphydryl residue of CK and maintain its catalytic unit for full activation. On the other hand, angiotensin converting enzyme (EC 3.4.15.1) is a kind of carboxypeptidase that liberates histidyl-leucine from angiotensin I or phenylalanyl-arginine from bradykinin at the C terminal. Recently, CK conversion factor, a certain kind of carboxypeptidase that converts the MM isozyme into three components, resulting in a loss of the activity, has been reported in plasma. Sulphydryl reagents including penicillamine reportedly inhibit CK conversion factor. In addition, one of the sulphydryl reagents, 2-mercaptoethanol, inhibits carboxypeptidase N (kinase I), and captopril is a potent inhibitor of angiotensin converting enzyme (kinase II). Although the effect of carboxypeptidase N or angiotensin converting enzyme on CK is not known, some carboxypeptidases, especially A or B, and proteinase K, have been reported to influence the sulphydryl group of CK and change the molecular configuration, resulting in a loss of activity. If this mechanism applies to angiotensin converting enzyme, inhibition of angiotensin converting enzyme with captopril may increase CK activity.

Whatever the mechanisms are, the captopril molecule contains the sulphydryl group, which interacts closely with muscle CK. We hope that another angiotensin converting enzyme inhibitor without a sulphydryl group soon will be available, so that the sulphydryl group's involvement in the toxic side effects of captopril, including CK elevations, can be confirmed or denied. Fortunately, any evidence of captopril-induced myopathy, as is seen during β-blockade, has not been found.

In our study, the elevated CK levels either decreased spontaneously despite continuous captopril administration in most patients or normalized quickly after medication was stopped in one patient. Although captopril is widely used because of its hypotensive efficiency as well as its acceptance by patients and is regarded as a first-line antihypertensive agent, it is also one of the first available agents to inhibit the endogenous enzymes. The long-term effect (i.e., 10–20 years) of endogenous enzyme blockade as well as of captopril’s sulphydryl group should be watched carefully.

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