Clinical Use of Captopril

To The Editor:

A recent article by Laragh, Case, Atlas, and Sealey in Hypertension describes the triphasic effects of captopril on blood pressure (BP). The authors provide some practical recommendations for the clinical use of the drug, about which we want to comment.

First, the authors state that the 90-minute response to the first single oral dose of captopril can often be used to predict the long-term benefit of the drug. Although we agree that this test has predictive value, we want to stress that it should be used carefully in patients with severe or accelerated hypertension. The test may even be dangerous in those patients when sodium depletion by dietary or diuretic therapy is present, since severe hypotension may ensue. Enthusiasm for the more potent forms of antihypertensive therapy has been tempered by the publication of Ledingham et al. They described 10 patients with accelerated and malignant hypertension who showed acute neurological signs when BP was rapidly lowered, three of them dying without neurological recovery. Hence, we would advocate an angiotensin II-infusion test to predict the long-term response, we concur that this test may even be dangerous in sodium-depleted patients.

Second, the authors state that “clinicians should not add other drugs to the regimen (i.e., captopril) between Days 2 and 7 because it is premature to judge its long-term value until after at least 1 week of treatment.” They make this statement in the context of the description of the triphasic nature of the antihypertensive action of captopril due to a transient defense of the preexisting BP by the nervous system. However, the possibility cannot be excluded that this rebound is angiotensin II-mediated. Oparil et al. have convincingly shown that in dogs the systemic vascular bed taken as a whole contains large amounts of angiotensin I-converting enzyme that is capable of rapid generation of angiotensin II without releasing the hormone into circulation. Leaving aside the exact mechanisms of rebound after the first dose of captopril, we would like to emphasize the possible danger of this rebound. One of our patients developed transient neurological signs after the first oral dose of captopril during the subsequent rebound of BP. Therefore, the message should be that clinicians should add antihypertensive agents — albeit temporarily — in case preexisting BP is high and there is a threat of rebound.

Finally, the authors state that “patients whose BP is controlled with captopril are, in general, uniquely free of side effects.” It is obvious that the authors have misquoted “side effects” and confused it with well-being, as can be deduced from the context of their discussion. In a recent survey by the Squibb Company (as cited in Lancet) it appeared that 11% of the patients on captopril developed skin rashes and 5%, loss of taste. More serious side effects reported include agranulocytosis and nephrotic syndrome. In our group of 89 patients treated for up to 30 months with captopril, five of them developed proteinuria, a figure comparable with that reported by Case et al. Hence, one really cannot state that the drug is uniquely free of side effects, whatever the clinical significance of the side effects turns out to be.

Authors’ Response:

While we are pleased that Drs. Hoornije and Donker confirm our report that the blood pressure (BP) response to the first dose of captopril can be used to predict the long-term response, we concur that this test can be potentially dangerous in sodium-depleted patients. In fact, our initial experience with captopril published in 1978 described a hypotensive episode following captopril in a patient with accelerated hypertension who had previously received a dose of furosemide. The hypotension was promptly and safely reversed by placing the patient in the head-down Trendelenberg position and infusing normal saline. As a result of this and several other similar experiences, as a standby procedure we now are prepared to infuse saline into patients who need immediate captopril treatment, particularly those who have received a diuretic or have any question of being volume-depleted. For the same reason, too, we withdraw diuretic therapy for at least several days before starting captopril in other patients who are not in urgent need of antihypertensive therapy.
However, we are firmly opposed to the proposal of infusing angiotensin II in the event of captopril-induced hypotension. As one of the most potent vasoconstrictors known to occur in man, angiotensin II in even minimal excess could raise the BP drastically. Our earlier experience with saralasin withdrawal and rebound hypertension provided clear evidence for the deleterious effects of an abrupt rise in angiotensin II levels and BP. Moreover, there is evidence for enhanced sensitivity of regional vascular resistance to angiotensin II during converting enzyme blockade.

With respect to the addition of other drugs during the secondary rise in BP, this is really a matter of clinical judgment. Certainly, in high-risk patients with an exaggerated rebound of BP, another drug should be added to control the BP. As the secondary pressure rise subsides after a week or so, however, the added drug may no longer be needed. In our experience, the average patient with uncomplicated mild-to-moderate hypertension does not require this approach. Whatever the mechanism for the transient return of BP toward the pretreatment level, it does not respond to increases in the captopril dose (unpublished observations). Therefore, it is apparently not due to increased angiotensin formation, since the mechanism is inaccessible to additional converting-enzyme blockade with captopril.

Finally, the initial experience with captopril has indicated that toxicity does at times occur, particularly in patients with underlying renal or collagen vascular disease. As we are preparing to report our 4 years' experience with captopril used in about 200 patients, several important trends are now becoming clear:

1. The initial doses of drug (400 to 1000 mg/day) are excessive. Most patients can be successfully managed on 200 to 300 mg/day or less. Even after large reductions in BP following the first dose, there can be a secondary rebound phase of drug resistance seen in many patients, lasting for 1 week or longer. The original dose-ranging studies were conducted during this "resistant" phase, resulting in final doses that were excessive since they could be subsequently reduced in the majority of patients without losing control of pressure. We currently use between 50 to 150 mg/day in most patients with normal renal function.

2. With regard to your point about "side effects," as our paper indicates we define this term as unwanted physiologic accompaniments such as reflex tachycardia, impaired mental function, impotence, or postural hypotension. Clearly, captopril produces fewer of these. We refer to proteinuria and agranulocytosis as true toxic effects.

3. In this context, the true toxicity of captopril appears dose-related and is enhanced by the presence of renal insufficiency. Now that lower doses are being used, the incidence of rash, loss of taste, proteinuria, and leukopenia has become minimal.

References

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S J Hoornije and A J Donker

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