Comparative Effects of Teprotide and Captopril

To The Editor:

I read with interest the recent report in Hypertension by Dr. Crantz and his colleagues in which the vascular and hormonal effects of teprotide and captopril were compared in patients with normal renin essential hypertension. At the doses used, captopril was observed to cause a greater depressor response than teprotide. The authors conclude from their data that the mechanism of action of captopril is different from that of teprotide. They further infer that a mechanism in addition to inhibition of angiotensin II (AI1) generation must have an important contribution to the hypotensive action of captopril.

There appear to be several serious flaws in such a formulation. Most important, the administered doses of these two agents were judged to be equivalent on the basis of nearly equal absolute changes in plasma renin activity (PRA) and plasma AI1 levels. However, it is noted that the mean pretreatment plasma AI1 level of the teprotide group was significantly higher than that of the captopril-treated group (33.3 ± 3.3 vs 19.9 ± 3.4 pg/ml, p < 0.01). Whereas the absolute fall of AI1 was similar in the two treatment groups, the percent change in AI1 levels had to be markedly greater in the captopril group (about 33% vs 21%). Although the individual patient data are not provided, it seems likely that this difference was statistically significant. The mean circulating level of AI1 during teprotide administration had to be about twice as high as that of the captopril group (26 vs 13 pg/ml). Thus, it is most probable that the apparent difference in the hypotensive effect of the two drugs derives primarily from the fact that nonequivalent doses were administered.

Interestingly, the authors contend that the higher pretreatment AI1 levels in the teprotide group should if anything enhance the relative depressor response to this agent. Their argument is based on the well-documented finding that shows a positive correlation between vascular responsiveness to renin-blocking drugs and pretreatment AI1 levels or PRA. However, all such studies, including previous work by the same study group, have investigated the relationship of hypotensive response to control AI1 or PRA with only one renin inhibitor at a time. There is no reason to infer that this relationship holds when nonequivalent doses of two such agents are compared in different groups of patients. An effectively lower dose of teprotide would not be expected to have the same depressor effect as a higher dose of captopril, regardless of the pretreatment PRA or AI1 level.

The authors have attempted to control for possible pretreatment differences by determining, for each patient on a previous date, the dose of captopril that resulted in a decrement of 15 mm Hg of diastolic blood pressure (DBP). However, any of a number of factors that are difficult to precisely control could alter vascular responsiveness to captopril in the interim between the dose-titration day and the study date. These might include blood pressure, salt balance, PRA, or AI1 levels. Despite these potential problems, the investigators were moderately successful with the captopril group, in that about 12 of 21 patients achieved the goal of a 15 mm Hg drop in DBP following administration of the previously determined dose (cf. the authors' fig. 1). Such was not the case in the teprotide group, where apparently only 3 of 10 patients achieved the goal of a 15 mm Hg decline in DBP (authors' fig. 1). This is especially puzzling because the dose titration of teprotide, in contrast to captopril, was performed during the actual study period, thereby eliminating most of the potential pitfalls inherent in the captopril-dosing method. One would have to question whether maximum doses of teprotide were actually utilized to reach the goal decrement in DBP. Furthermore, another possible confounding factor is suggested by the relatively large variance of the pretreatment DBP in the teprotide group. With a mean control DBP of 91 ± 8 mm Hg (n = 10), the calculated standard deviation, 25 mm Hg, suggests that perhaps half or more patients in the teprotide group were well within the normotensive range (DBP < 90 mm Hg) on the study day.

It is, therefore, difficult to understand how the findings presented in this report in any way support the authors' contention that teprotide and captopril have different mechanisms of actions, or that an effect other than inhibition of AI1 plays the major role in such action.

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References

AUTHORS’ RESPONSE:

Dr. Ruddy raises several interesting points related to our previously published manuscript in Hypertension. Indeed, in reading his letter, we had a sense of déjà vu because each of the points he raised we had raised ourselves after the initial review of our data. Thus, we also were concerned about the problems inherent in a study where two drugs are administered by different routes and to two different patient populations. As suggested by Dr. Ruddy, we evaluated whether the observed differences in hormonal responses could be explained by differences in any of these variables. As noted in the results section, we determined whether the differences could be explained by differences in basal blood pressure, blood pressure response to the drugs, or basal angiotensin II levels. We also assessed the effect of the first dose versus successive doses of the agent. In addition to these concerns raised by Dr. Ruddy, we also assessed whether the fact that the drugs were not administered to the same individual could have explained the difference in hormonal response. Yet, when we evaluated the hormonal responses to these two agents, controlling for each of these four variables, the differences persisted.

We appreciate the opportunity to respond to Dr. Ruddy’s letter since apparently the discussion section of our paper did not highlight the fact that, even when each of these variables was evaluated separately, there was still a significant difference in the hormonal response to these two converting enzyme inhibitors, suggesting that the factors mediating the vascular responses to these agents may be different. Furthermore, this study raises the possibility that the development of converting enzyme inhibitors more specific for each action of this enzyme may be possible.

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Error in Reference Citation

Editor’s Note: Dr. Caroline Bedell Thomas has called to our attention an error in the second reference in the article by Fink et al. on page 319 of the May-June 1980 issue of Hypertension. The year of publication was 1944, not 1954; the reference should read as follows:

Thomas CB: Experimental hypertension from section of moderator nerves: Relationship of the acute pressor response to the development and course of chronic hypertension. Bul Johns Hopkins Hosp 74 (6): 335-377, 1944

Dr. Thomas also points out that ref. 1 of Fink’s paper, citing Heyman’s English edition published in 1958, was preceded by his original edition published in Paris in 1933.

H.P.D.
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doi: 10.1161/01.HYP.3.2.277

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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http://hyper.ahajournals.org/content/3/2/277.citation

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