Plasma Renin Substrate Concentration during Chronic Propranolol Therapy

To the Editor:

The review by Gordon" concerning a positive correlation between plasma renin substrate concentration (PRS) and blood pressure (BP) prompted us to evaluate our PRS data from a randomized double-blind study on the antihypertensive effect of enalapril (MK 421) compared to propranolol. Twenty-two patients with essential hypertension were treated in subsequent 4-week periods by placebo and 40, 80, and 120 mg b.i.d. propranolol (n = 9); or by placebo and 5, 10, and 20 mg b.i.d. enalapril (n = 13). If BP decreased insufficiently, 25 mg s.d.d. hydrochlorothiazide (HCT) was added to the highest dose (n = 7 and n = 10, respectively).

At the end of each period (in the placebo period also after 2 weeks), before the morning dose was given (i.e., about 12 hours after the previous dose) and after 90 minutes of upright stimulation, blood samples were taken for determination of angiotensin I and II (AI and All), plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma converting enzyme activity (CEA), and PRS. The BP was measured by Arteriosonde. PRA (normal range 0.20 to 1.20 pmol/liter/sec) and PAC (0.15 to 1.10 nmol/liter) were measured by standard radioimunoassay techniques. AI (10 to 80 pmol/liter) and All (5 to 50 pmol/liter) were measured by radioimunoassay after blood sampling with an inhibitor solution containing EDTA, captopril, and pepstatin, and a batch-wise Dowex resin extraction procedure. CEA (0.30 - 1.20 μmol/liter/sec) was measured by a colorimetric method, and PRS (0.90 to 1.05 μmol/liter) for men; 0.60 to 0.90 μmol/liter for women) by an antibody-trapping technique. Data were analyzed with Wilcoxon's test for paired observations.

In table 1, the mean arterial pressure (MAP) and the geometric means of the hormonal parameters are shown. PRA and All increased during enalapril therapy (p < 0.002), while PAC (p < 0.04) All, CEA (both p < 0.002), and MAP (p < 0.005) decreased. PRS did not change at the lower doses, but decreased at the highest dose (p < 0.01) and with the combined therapy (p < 0.02). PRA, All, and CEA decreased during propranolol treatment (p < 0.01), but returned to baseline values after the addition of HCT. MAP and PAC also decreased (p < 0.02, except for the lowest dose), and CEA did not change. In 13 of the 22 patients, the two pretreatment PRS concentrations were above the upper normal limit, which is in agreement with the observation of Walker et al." in hypertensive patients. During propranolol treatment, these high PRS levels increased even further (p < 0.01, except for lowest dose). We cannot explain this phenomenon, although a decrease in PRA cannot be the cause, as the increase in PRA after the addition of HCT still is accompanied by a high PRS.

Thus, all changes in the parameters were in the expected directions, with the exception of PRS. Our findings of an increased PRS in the presence of a decreased BP after chronic propranolol therapy has to our knowledge not been reported earlier and is at variance with the causal relationship suggested by Gordon."
LETTERS TO THE EDITOR

References
2. Workman RJ, Sussman CR, Burkitt DW, Liddle GW: Circulating levels of angiotensin I measured by radioimmunoassay in hypertensive subjects. J Lab Clin Med 1979;93:847-856

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AUTHOR'S RESPONSE:
I am pleased that Drs. Boer and Geyskes found my review article an incentive for additional study of the levels of renin substrate in essential hypertension. Their data on PRS values in patients treated with enalaprill show a clear correlation between the lowering of PRS and lowering of blood pressure, thus supporting the hypothesis of a possible causal relationship. Their data on such values in patients treated with propranolol show exactly the opposite, i.e., that increasing PRS values correlate with lowering of blood pressure. There are two obvious conclusions to be drawn from these data: 1) the hypothesis of a positive correlation between blood pressure and PRS is not valid in all circumstances; and 2) the mechanism of blood pressure lowering by propranolol is quite different from that of enalaprill. The finding of an actual increase in PRS with increasing doses of propranolol is quite surprising. It leads me to wonder if large increases of PRS may be found to coincide with undesirable side effects related to increased peripheral vasoconstriction, such as Raynaud's phenomenon, intermittent claudication, and peripheral gangrene, which occur in some patients treated with propranolol.

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Correction to Graph in September-October Supplement

TO THE EDITOR:
I enclose the corrected version of figure 7 of my paper in the Supplement of Hypertension concerning the Satellite to the European Milan Meeting. The error was in the second line of the illustration, which should be "... vs mean of 24 hours" and not "vs mean of 4 hours." (Hypertension 5 (suppl III): III-5-III-13, 1983; Mancia G: Methods for Assessing Blood Pressure Values in Humans.)

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FIGURE 7 Comparisons of the average 24-hour mean arterial pressure value with the average mean arterial pressure (MAP) values obtained during different hours (upper panel) or different 4-hour periods (lower panel) of the same 24 hours. Data are shown individually for 28 subjects in which 24-hour intraarterial blood pressure recordings were made. Each recording was analyzed by a computer that sampled the blood pressure trace every 60 msec to obtain the 24-hour average MAP value. The same analysis was performed to obtain hourly or 4-hour averages starting from midnight and advancing at half-hour steps (horizontal lines). The differences between the hourly or 4-hour averages and the 24-hour averages were plotted by considering the latter as the 0 reference value. (From Di Rienzo et al., unpublished data.)
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