Effects of Atenolol and Hydrochlorothiazide on Blood Pressure and Plasma Catecholamines in Essential Hypertension

MARTIN G. MYERS, M.D., F.R.C.P.(c),
AND JACQUES DE CHAMPLAIN, M.D., PH.D.

SUMMARY The antihypertensive effects of atenolol and hydrochlorothiazide were compared with placebo in a randomized, double-blind crossover study, with the blood pressure responses related to sympathetic nervous system activity. Twelve patients with essential hypertension were given atenolol (100 mg), hydrochlorothiazide (50 mg), and placebo as single daily doses, each for 6 weeks. Mean supine, standing, and post-exercise blood pressures (mm Hg) on atenolol (155/94, 152/95, 177/93, respectively) and hydrochlorothiazide (154/99, 150/103, 172/96) were lower \((p < 0.01)\) than corresponding placebo values (172/109, 166/113, 204/111) at 6 weeks. The role of the sympathetic nervous system in the antihypertensive actions of atenolol and hydrochlorothiazide was examined. The supine plasma norepinephrine on placebo was used as an index of sympathetic activity to categorize each patient’s “adrenergic status.” The six “hyperadrenergic” patients with high resting norepinephrine values (mean, 302 pg/ml) exhibited a greater \((p = 0.05)\) decrease in BP (-30/-20 mm Hg) on atenolol compared with the BP fall of -9/-11 mm Hg observed in the lower norepinephrine group (mean, 211 pg/ml). Resting plasma norepinephrine values did not predict the BP fall on hydrochlorothiazide. The “adrenergic status” of each patient as measured by the plasma norepinephrine concentration tended to be relatively constant regardless of therapy or the state of activity. In this study, atenolol was an effective antihypertensive agent comparable to hydrochlorothiazide in potency. Adrenergic status tended to predict the BP response to atenolol and was a relatively constant feature of the patients in all treatment phases. (Hypertension 5: 591-596, 1983)

KEY WORDS • atenolol • hypertension treatment • sympathetic activity • adrenergic receptors

ATENOLOL is a cardioselective beta-adrenergic receptor antagonist that has been shown to be an effective antihypertensive agent in patients with essential hypertension. Initial studies suggested that the drug had a relatively horizontal dose-response curve and subsequently an effective dosage range of 50–100 mg daily has been confirmed. The elimination half-life of atenolol (6–9 hours) and the relatively long duration of its antihypertensive action have made once daily dosing feasible.

During the past decade there has been considerable study and speculation on the importance of the sympathetic nervous system in the depressor effects of beta-blockers, including atenolol. Actions of these drugs on both the central and peripheral components of sympathetic function have been described and possible mechanisms postulated. One group has proposed that hypertensive patients with high levels of sympathetic activity as characterized by elevated resting plasma norepinephrine concentrations respond better to beta-blocker therapy. In the present study, we have examined this hypothesis as part of a double-blind crossover comparison study of the antihypertensive effects of atenolol and hydrochlorothiazide compared with placebo in patients with essential hypertension.
Methods

The study population consisted of 12 patients with essential hypertension who successfully completed the full protocol. Three additional patients were entered but had to be withdrawn because of a variety of reasons unrelated to atenolol therapy. The mean age of the 12 participants was 52.8 years; eight were men. Secondary causes of the hypertension were excluded following routine clinical, biochemical, and radiologic evaluations including renal arteriography, if indicated. Entry criteria were as follows: diastolic blood pressure = 100 mm Hg or greater (mean of two readings on two separate occasions; no evidence of accelerated or malignant hypertension; absence of second- or third-degree heart block; and no history of hepatic or renal disease, diabetes, alcoholism, asthma, myocardial infarction, stroke, congestive heart failure, or angina pectoris. Patients with a resting heart rate under 50 bpm were also excluded as were individuals needing other medications known to affect blood pressure or sympathetic nervous function.

The study design was a double-blind crossover comparison between atenolol 100 mg daily, hydrochlorothiazide 50 mg daily, and placebo. Tablets were administered using a "double dummy" technique so that each patient received two tablets daily in the following combinations: placebo atenolol + active hydrochlorothiazide, active atenolol + placebo hydrochlorothiazide, and both placebo. Adherence to therapy was estimated by counting the number of returned tablets on each visit. Each treatment phase consisted of 6 weeks, with the patients attending at three weekly intervals. Prior to entry, each subject underwent a complete history and physical examination. A standard 12 lead electrocardiogram was performed as were the following biochemical tests: complete blood count, serum electrolytes, creatinine, bilirubin, cholesterol, uric acid, alkaline phosphatase, SGOT, BUN, urinalysis and microscopic examination. These parameters were repeated at the end of each 6-week treatment period.

At each visit, the blood pressure and heart rate were recorded in duplicate after 5 minutes' supine and 2 minutes' erect using a Random Zero sphygmomanometer (Gelman Hawkesley Ltd, Sussex, United Kingdom) and ECG monitor, respectively. Any adverse effects volunteered by the patient or other medication given since the previous visit were recorded. After 6 weeks on each treatment, the patient underwent treadmill exercise, achieving 80% of their predicted maximum heart rate using the Bruce protocol. Blood pressure was recorded immediately following the exercise.

An indwelling intravenous heparin lock device was used to obtain plasma samples for norepinephrine and epinephrine following 30 minutes of supine rest, 10 minutes erect, and after treadmill exercise at the end of each 6-week treatment period. Norepinephrine and epinephrine concentrations were determined according to the method of Peuler and Johnson. Differences in blood pressure, heart rate, and plasma catecholamines among the three periods were evaluated by means of analysis of variance. The blood pressure response to atenolol and hydrochlorothiazide was examined in patients with either high or normal adrenergic tone as determined by the supine norepinephrine value during the placebo period. In the absence of a control population, the median value of the plasma norepinephrine data was arbitrarily used to separate the "high" from "normal" adrenergic status.

Table 1. Clinical Aspects of Patients on Entry Including Plasma Norepinephrine Concentrations while Supine on Placebo

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Pretreatment supine BP (mm Hg)</th>
<th>After 6 wk placebo supine BP (mm Hg)</th>
<th>HR (bpm)</th>
<th>Supine plasma norepinephrine on placebo (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>51</td>
<td>193/108</td>
<td>209/117</td>
<td>80</td>
<td>293*</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>35</td>
<td>158/107</td>
<td>154/92</td>
<td>72</td>
<td>219</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>45</td>
<td>172/106</td>
<td>171/116</td>
<td>80</td>
<td>186</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>58</td>
<td>168/111</td>
<td>173/116</td>
<td>84</td>
<td>346*</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>56</td>
<td>166/101</td>
<td>159/109</td>
<td>70</td>
<td>312*</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>55</td>
<td>225/107</td>
<td>208/111</td>
<td>74</td>
<td>198</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>46</td>
<td>174/111</td>
<td>168/112</td>
<td>72</td>
<td>164</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>48</td>
<td>170/99</td>
<td>180/119</td>
<td>88</td>
<td>292*</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>59</td>
<td>159/100</td>
<td>159/103</td>
<td>60</td>
<td>241</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>64</td>
<td>181/115</td>
<td>178/111</td>
<td>110</td>
<td>285*</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>58</td>
<td>169/101</td>
<td>161/108</td>
<td>76</td>
<td>255</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>58</td>
<td>149/100</td>
<td>156/93</td>
<td>68</td>
<td>286*</td>
</tr>
</tbody>
</table>

Mean ± SEM

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>53 ± 2</td>
<td>174 ± 6/106 ± 2</td>
<td>173 ± 5/109 ± 3</td>
<td>78 ± 4</td>
<td>256 ± 16</td>
<td></td>
</tr>
</tbody>
</table>

*Denotes the "hyperadrenergic" patients.
Table 2. Effect of Atenolol, Hydrochlorothiazide, and Placebo on Blood Pressure (mm Hg) Heart Rate (bpm), Plasma Norepinephrine and Epinephrine Concentrations (pg/ml) in 12 Patients Completing the Three Crossover Phases

<table>
<thead>
<tr>
<th></th>
<th>Atenolol treatment period (wk)</th>
<th>Hydrochlorothiazide treatment period (wk)</th>
<th>Placebo treatment period (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Supine BP</td>
<td>153/94†</td>
<td>156/101*</td>
<td>172/108</td>
</tr>
<tr>
<td>HR</td>
<td>61†</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>—</td>
<td>327*</td>
<td>—</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>—</td>
<td>63</td>
<td>—</td>
</tr>
<tr>
<td>Standing BP</td>
<td>150/96*</td>
<td>152/95†</td>
<td>169/112</td>
</tr>
<tr>
<td>HR</td>
<td>65</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>422</td>
<td>489</td>
<td>—</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>88</td>
<td>72</td>
<td>—</td>
</tr>
<tr>
<td>Exercise BP</td>
<td>177/93†</td>
<td>172/96*</td>
<td>—</td>
</tr>
<tr>
<td>HR</td>
<td>101†</td>
<td>132</td>
<td>—</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>1351*</td>
<td>951</td>
<td>—</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>144†</td>
<td>89</td>
<td>—</td>
</tr>
</tbody>
</table>

Statistical significance of difference from corresponding placebo value: *p < 0.05; †p < 0.01; ‡p < 0.001.

Results

The mean value for the pre-entry supine blood pressure was 174/106 mm Hg and on standing 164/108 mm Hg (table 1). These recordings were consistent with pressure measurements taken after 6 weeks of placebo therapy. Both atenolol 100 mg daily and hydrochlorothiazide 50 mg daily produced a significant reduction in blood pressure in both the supine and erect positions after 3 and 6 weeks of therapy (table 2). Blood pressure recordings taken immediately after treadmill exercise were also significantly reduced by both of these drugs. Diastolic pressures on atenolol tended to be slightly lower than those recorded during hydrochlorothiazide therapy but the differences were small and significant (p < 0.05) only at 6 weeks in the erect position. Atenolol produced significant reductions in mean supine, erect, and exercise heart rates compared to both placebo and hydrochlorothiazide values.

Plasma norepinephrine concentrations were significantly higher when measured in the supine position while on hydrochlorothiazide and after exercise on atenolol compared with corresponding placebo values (table 2). Similarly, mean epinephrine concentrations were significantly elevated after exercise on atenolol therapy.

The "adrenergic status" of each patient was constant regardless of the treatment phase or activity (table 3). For example, patients with high plasma norepinephrine concentrations while supine had relatively high values while erect or after exercise. The supine norepinephrine concentrations on placebo also correlated significantly with the corresponding values after exercise on atenolol (p < 0.01) and hydrochlorothiazide (p < 0.001).

The supine norepinephrine value on placebo was used to characterize the adrenergic status of the patients. The six individuals who were classified as hyperadrenergic (plasma norepinephrine 285 pg/ml or greater) had a mean concentration of 302 pg/ml compared with a mean value of 211 pg/ml in the "normal adrenergic" group. The "hyperadrenergic" patients exhibited a fall in blood pressure of — 30/— 20 mm Hg on atenolol whereas the "normal adrenergic" group had a BP reduction of only — 9/— 11 mm Hg.

The "adrenergic" status did not predict the response to hydrochlorothiazide and patients with higher

Table 3. Coefficients of Correlation for Norepinephrine and Epinephrine Values in the 12 Subjects While Supine, Erect, and After Exercise

<table>
<thead>
<tr>
<th></th>
<th>Coefficient of correlation (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
</tr>
<tr>
<td>supine vs erect</td>
<td>0.679*</td>
</tr>
<tr>
<td>supine vs exercise</td>
<td>0.718†</td>
</tr>
<tr>
<td>erect vs exercise</td>
<td>0.602*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
</tr>
<tr>
<td>supine vs erect</td>
<td>0.805†</td>
</tr>
<tr>
<td>supine vs exercise</td>
<td>0.583*</td>
</tr>
<tr>
<td>erect vs exercise</td>
<td>0.566</td>
</tr>
</tbody>
</table>

* p < 0.05; † p < 0.01; ‡ p < 0.001.
epinephrine values did not exhibit greater depressor effects with either drug. In the “hyperadrenergic” patients, the mean supine plasma norepinephrine concentrations on placebo (302 pg/ml) was reduced slightly to 292 pg/ml (p > 0.05) during atenolol therapy. The mean (± SEM) supine heart rate on placebo at 6 weeks was higher in the “hyperadrenergic” patients (83.3 ± 6.2 bpm) than in the “normoadrenergic” group (72.3 ± 2.8 bpm) but the difference was not statistically significant.

Compliance with therapy was excellent with over 90% of the prescribed tablets being consumed. Twelve of the 15 patients entering the study completed all three treatment phases. One patient was withdrawn because of persisting severe hypertension during the initial two phases (atenolol and hydrochlorothiazide). Another individual was removed from the trial after 3 weeks on the request of his family doctor. The third withdrawal occurred when the patient developed a recurrence of her chronic anxiety state as a result of her participation in the research study.

Mean serum concentrations of potassium (mEq/liter), uric acid (mg/dl) and bicarbonate (mmol/liter) on placebo (3.9, 5.5 and 24.3 respectively) were significantly altered by hydrochlorothiazide therapy. In the present study, these drugs were well tolerated by patients and each reduced the mean blood pressure substantially in the supine and erect positions and after treadmill exercise. Atenolol lowered the diastolic blood pressures somewhat more than hydrochlorothiazide. This finding is consistent with previous reports which showed a greater diastolic blood pressure fall on atenolol compared with chlorothalidone 25 mg daily and bendrofluazide 5 mg daily. 13 It is likely that the preferential effect of atenolol on the diastolic blood pressure resulted from differences in the mechanisms of action of the two classes of drugs.

The magnitude of the depressor response to atenolol was comparable to findings from other studies 1, 2, 12, 13 as was the degree of beta-blocker induced bradycardia.

Recent studies have shown that norepinephrine values may be determined not only by spillage from the synaptic cleft of the nerve terminal but also by changes in norepinephrine clearance in the elderly may explain the positive correlation observed between age and the plasma norepinephrine concentration. 21, 22 However, others have not observed such a correlation in hypertensive patients. 8, 23

The clearance of norepinephrine from the circulation may also depend upon changes in cardiac output with resultant alterations in blood flow to the liver and lungs, major sites of norepinephrine elimination. Brown et al. 24 have reported that the infusion of isoproterenol increases norepinephrine elimination whereas others 25, 26 have shown that beta-adrenoceptor antagonism will have the opposite effect. Thus, the higher post-exercise norepinephrine values on atenolol may have resulted from the relatively lower exercise-induced augmentation of cardiac output during beta-blockade. Furthermore, atenolol may only cause an apparent increase in sympathetic activity with the higher norepinephrine values resulting from a fall in clearance rather than an increase norepinephrine spillage from the synaptic cleft. If true, this phenomenon would explain the paradox of a drug lowering blood

Discussion

Atenolol appears to be an effective antihypertensive agent of at least equal potency to usual doses of hydrochlorothiazide. In the present study, these drugs were well tolerated by patients and each reduced the mean blood pressure substantially in the supine and erect positions and after treadmill exercise. Atenolol lowered the diastolic blood pressures somewhat more than hydrochlorothiazide. This finding is consistent with previous reports which showed a greater diastolic blood pressure fall on atenolol compared with chlorothalidone 25 mg daily and bendrofluazide 5 mg daily. 13 It is likely that the preferential effect of atenolol on the diastolic blood pressure resulted from differences in the mechanisms of action of the two classes of drugs. The clearance of norepinephrine from the circulation may also depend upon changes in cardiac output with resultant alterations in blood flow to the liver and lungs, major sites of norepinephrine elimination. Brown et al. 24 have reported that the infusion of isoproterenol increases norepinephrine elimination whereas others 25, 26 have shown that beta-adrenoceptor antagonism will have the opposite effect. Thus, the higher post-exercise norepinephrine values on atenolol may have resulted from the relatively lower exercise-induced augmentation of cardiac output during beta-blockade. Furthermore, atenolol may only cause an apparent increase in sympathetic activity with the higher norepinephrine values resulting from a fall in clearance rather than an increase norepinephrine spillage from the synaptic cleft. If true, this phenomenon would explain the paradox of a drug lowering blood
pressure while simultaneously appearing to increase sympathetic activity. However, not all studies are in agreement with the observations of Brown et al. In seven normal subjects and ten patients with borderline hypertension, Vincent et al. have recently reported that isoproterenol caused an increase in the plasma concentration of norepinephrine. These conflicting results must be investigated further before the importance of changes in clearance to the plasma concentration of norepinephrine is fully understood.

The possible role of norepinephrine clearance as a determinant of the amount of circulating norepinephrine does not preclude the use of the plasma norepinephrine value as a measure of sympathetic activity. In our group of predominantly middle-aged hypertensive patients under standardized conditions, the plasma norepinephrine concentration was a predictor of the blood pressure response to atenolol. This finding is consistent with an earlier observation that "hyperadrenergic" patients exhibited greater blood pressure reductions on either metoprolol or propranolol therapy. The detection of a similar relationship for atenolol in this relatively small number of patients suggests that adrenergic status is likely a major determinant of the blood pressure response to beta-blockers. Furthermore, beta-adrenoceptors may themselves play a more critical role in the maintenance of hypertension in the "hyperadrenergic" hypertensive population.

Even under conditions where cardiac output and norepinephrine clearance may change, it may still be possible for the plasma norepinephrine concentration to reflect relative levels of sympathetic activity. For example, patients with higher supine plasma norepinephrine values on placebo in our study tended to have proportionately higher values while standing and after exercise. The rank order of norepinephrine status was also maintained during atenolol and hydrochlorothiazide therapy. Furthermore, the supine plasma norepinephrine concentration on placebo correlated significantly with the corresponding post-exercise values on both atenolol and hydrochlorothiazide. These observations suggest that alterations in cardiac output and other factors affecting norepinephrine clearance may exert a proportionately similar effect on the plasma norepinephrine concentration such that those individuals with higher norepinephrine values on placebo will continue to exhibit relatively high values regardless of atenolol or hydrochlorothiazide therapy.

The combined results of the present study and earlier reports suggest that all beta-blockers do not exert the same effect on sympathetic nervous system function as measured by plasma norepinephrine. Drugs without intrinsic sympathomimetic activity such as propranolol, metoprolol and atenolol tend to increase norepinephrine values, particularly after exercise. However, certain sub-groups such as "hyperadrenergic" hypertensive patients may actually exhibit a fall in plasma catecholamines coincidental with the pronounced reduction in blood pressure. One might speculate that "adrenergic" status may be a useful index of responsiveness prior to the initiation of antihypertensive therapy. Furthermore, the sympathetic profile of patients appears to be relatively consistent under a variety of conditions when determined by a single plasma norepinephrine sample, regardless of alterations in clearance.

Acknowledgment
The authors thank A. G. McMillan and E. Roberts for technical and secretarial assistance.

References
17. Distler A, Kein H, Cordes U, Philipp T, Wolff HP: Sympa-


Effects of atenolol and hydrochlorothiazide on blood pressure and plasma catecholamines in essential hypertension.
M G Myers and J de Champlain

Hypertension. 1983;5:591-596
doi: 10.1161/01.HYP.5.4.591

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/4/591

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/