Clinical and Biochemical Effects of Spironolactone Administered Once Daily in Primary Hypertension
Multicenter Sweden Study

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SUMMARY In a prospective, double-blind, intrahospital, cross-over, placebo-controlled multicenter study, clinical and biochemical effects of once daily postprandial dose regimens of 50, 100, and 200 mg spironolactone were investigated in 45 outpatients with primary hypertension, WHO (World Health Organization) Stage I-II. Each of the three active therapy periods, which were randomly allocated to patients, were of 2 months' duration, with intervening placebo periods. Clinical and biochemical parameters, including furosemide-stimulated plasma renin activity (PRA), were recorded at regular intervals. All three spironolactone doses resulted in statistically significant blood pressure (BP) reductions independent of initial pretreatment levels and yielded satisfactory BP control in more than half of the patients. The 200 mg daily dose of spironolactone was found to be more effective than 50 but not 100 mg. When, correlating blood pressure response (ΔMAP) to PRA, the profiling for positive spironolactone responders was characterized by high age and low PRA, irrespective of sex. Spironolactone therapy resulted in decreased serum sodium and magnesium values; potassium, creatinine, urate, and triglyceride levels were increased. However, all treatment values were within normal ranges. Side effects were infrequent and mainly of endocrine nature.

KEY WORDS • age • primary hypertension • single dose • double-blind study • spironolactone

THE ALDOSTERONE antagonist spironolactone has been used in the treatment of hypertension for more than a decade. Therapeutic efficacy has been demonstrated both with spironolactone as the sole therapy and when used concomitantly with thiazides, methyldopa, and beta-adrenergic blocking agents.

The aim of the present multicenter study is to investigate the effects of once-daily regimens of 50, 100, and 200 mg spironolactone in outpatients with mild or moderate primary (essential) hypertension. Special reference is made to dose-response relationships between blood pressure (BP) changes, demographic, clinical, and biochemical parameters, patient compliance, and side effect incidence. Furthermore, individual response to spironolactone is correlated with plasma renin activity (PRA).

Material and Methods

Admission to the study was restricted to patients under 75 years of age who presented diastolic phase 5 blood pressures (DBPs) between 105 and 135 mm Hg as a means of three measurements after 10 to 15 minutes of supine rest following a run-in period of 4 weeks.

The patients were recruited from the outpatient units in Dalby, Lund, Jönköping, Linköping, and Västerås, Sweden. All 50 patients included had untreated primary hypertension, 28 belonged to Stage I and 22 to Stage II according to WHO classification. No patients had diabetes mellitus, hepatic, or renal disorders. Five patients did not complete the whole trial for reasons to be described later. Thus the final patient population comprised 45 patients, 24 men and 21 women whose mean age was 52.0 ± 8.4 years (range, 36 to 73 years).
Study Procedures

The investigation was conducted as a double-blind, intraindividual, cross-over study with active therapy periods separated by placebo periods of 1 or 2 months' duration. Each patient received spironolactone (Aldactone, Searle) or a placebo in one identical appearing tablet taken daily with breakfast. Patients were randomly allocated to consecutive treatment periods of 50, 100, and 200 mg spironolactone after an initial 1 month's placebo period (fig. 1).

The duration of each active treatment period was 8 weeks, with clinical and biochemical examinations performed at intervals of 4 weeks. Each patient completed three active treatment periods. The duration of the entire investigation was 11 months per patient, with a 4 weeks' placebo period at the end of the study. Patient adherence to the study protocol procedures was checked by measurements of plasma cortisol by a fluorometric method in which spironolactone cross-reacts with cortisol, thus yielding high cortisol levels. Spontaneously reported side effects were recorded, and evidence of gynecomastia and menstrual irregularities were especially investigated by the physicians.

Anthropometric Measurements

Height and weight were measured following WHO recommendations. Index of obesity was calculated as weight (kg)/height² (m) according to Zilva and Nicholson.[12] Arm circumference was measured at the middle of the BP cuff and recorded to the nearest 0.5 cm.

Blood Pressure and Heart Rate Measurements

Blood pressures were recorded by the same nurse in each hospital unit from 8 to 11 a.m. A mercury manometer was used, and the BP was measured after the patient had rested 10 to 15 minutes in the supine position and then stood upright for 2 minutes, as previously described.[14] Heart rate was counted as beats/min from the radial pulse during a 30-second period. Blood pressure and heart rate were recorded at the monthly control examinations (fig. 1). In those study periods comprising 8 weeks of active or placebo treatment, the last recordings were used for analysis.

Pretreatment BP levels for the whole clinical population (n = 45) and for the patients randomly allocated to the three respective spironolactone doses are shown in table 1.

It is evident that BPs were constant during the "run-in" period. There was a significantly lower systolic blood pressure (SBP) (p < 0.01) and DBP (p < 0.01) during the initial placebo period and in the placebo periods preceding the different treatments as compared to the "run-in" period. However, BPs both in supine and upright positions — preceding the different spironolactone therapy periods — were of equal magnitude. Thus, the study design allowed an evaluation of the efficacy of the three spironolactone treatments in lowering the BPs. To evaluate whether satisfactory BP reduction was achieved, a comparison was made with a reference population from which the present patients originated. The mean BP plus one standard deviation for sex and actual age-group was considered to be well within the border of normality and therefore chosen as the target BP level.

Biochemical Variables

The following biochemical analyses were performed during the initial and final placebo periods: S-sodium, S-potassium, S-magnesium, S-creatinine, S-urate, fB-glucose, fS-cholesterol, and fS-triglycerides. Serum sodium, potassium and creatinine were determined at the end of each active period and during the intervening placebo periods. Furthermore, S-urate, fB-glucose, fS-cholesterol, and fS-triglycerides were determined at the end of the last two active periods.

All biochemical analyses were performed by routine methods used at the respective hospital departments according to current Swedish laboratory standards.

Plasma Renin Activity (PRA)

PRA was measured during basal conditions following 1 hour of complete rest from 8–9 a.m. (“basal PRA”), after 3–4 hours ambulation from 11 a.m. till noon (“upright PRA”), and 3–4 hours after oral administration of 80 mg furosemide (LASIX), at 3–4 p.m. (“stimulated PRA”). The values from these three determinations are described as the PRA-furosemide test.[18] PRA was determined with a radioimmunoassay method described by Fyhrquist et al.,[14] which measured the amount of angiotensin I (A1) generated during optimal incubating conditions at pH 6.0 and with minimal dilution (10%) of plasma. Values are given as the amount A1 generated per litre per hour (pkat/liter) according to the SI-unit system applied.

In the present investigation, repeated measurements of upright PRA (PRAu) were performed to check the reproducibility of PRAu in the individual patient as well as to estimate possible "carry-over" effects of spironolactone. The initial basal PRA (0.50 ± 0.63 pkat/liter) and upright PRA (0.64 ± 0.84 pkat/liter) were unchanged at the end of the study (0.64 ± 0.46 and 0.69 ± 0.69 pkat/liter respectively), indicating a good reproducibility and no carry-over effect after 4 weeks off treatment. Thus, the intervening placebo
periods were long enough to exclude interference of spironolactone. All PRA determinations were performed by the same two laboratory technicians.

Statistical Methods

Standard statistical methods were applied to determine mean values (M) and standard deviations (SD). The x^2 goodness-of-fit test was used to determine if the results obtained were normally distributed. Thereby, the parameters analyzed all those qualified for further statistical calculations using mean values and correlation coefficients. Differences between means of BPs, heart rates, and biochemical values from the various treatment periods were analyzed with the Student's t test. Correlations between AMAP, i.e., dose regimens as a yardstick (AMAP 18, 19, and 21 mm Hz for 50, 100, and 200 mg spironolactone respectively), "good" and "bad" responders were arbitrarily classified. Thereafter, the actual mean AMAP, mean arterial pressure, and loge PRA values were calculated and expressed as bivariate correlation coefficients. Correlation between dichotomized AMAP and PRA was determined and expressed as point-biserial coefficients. Significance of correlation coefficients were measured using t tests. Dose-dependent BP changes were analyzed for trends in a 2 × 3 contingency table. All p values were considered significant when smaller than 0.05.

Results

All three treatment periods with spironolactone resulted in reduced BP levels (p < 0.001) as compared to the respective preceding placebo periods (tables 1 and 2). Spironolactone 200 mg daily lowered mean SBP more than 50 mg (p < 0.05) but not more than 100 mg in the supine position (table 2). In the upright position 200 mg spironolactone produced a lower mean SBP (p < 0.01) than with both 100 and 50 mg.

However, the three treatment regimens decreased the DBP to the same extent.

Irrespective of initial BP levels, the three different doses of spironolactone had about identical BP lowering effects. The cumulative percentage distributions of DBPs and SBPs at the start of study, during placebo treatment, and during active treatment (combined for 50, 100, and 200 mg) are illustrated in figure 2.

A SBP and DBP level corresponding to the mean (M) plus 1 standard deviation (SD) for a defined population from Southern Sweden was reached by approximately half of the treated patients (table 3).

In this respect, the three dose regimens were equally effective (x^2-test for trend not significant).

The degree of obesity did not correlate with the BP-lowering effect of spironolactone, calculated as AMAP (r = 0.05 with n = 42). Spironolactone administration caused no significant weight reduction, the average weights being 80.0 ± 13.8 kg before and 79.1 ± 13.1 kg during treatment.

Heart rate was increased by spironolactone only in the upright position from 79 ± 8 to 83 ± 9 beats/min (p < 0.05) and to the same extent with each of the dosages administered.

The initial PRA (basal, upright, and stimulated) was consistently inversely correlated with the antihypertensive effect (ΔMAP) of spironolactone, irrespective of the doses applied, as shown in table 4 and illustrated for 200 mg of spironolactone in figure 3.

By using the mean ΔMAP in the three different dose regimens as a yardstick (ΔMAP 18, 19, and 21 mm Hz for 50, 100, and 200 mg spironolactone respectively), "good" and "bad" responders were arbitrarily classified. Thereafter, the actual mean ΔMAP, mean arterial pressure, and loge PRA values were calculated and expressed as bivariate correlation coefficients.

table 1. Blood Pressure Levels During Run-in and Placebo Periods in 45 Patients Completing the Study

<table>
<thead>
<tr>
<th>Period</th>
<th>Supine</th>
<th>Upright</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>Run-in</td>
<td>n</td>
<td>(mean ± sd) mm Hg</td>
</tr>
<tr>
<td>period:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>45</td>
<td>185 ± 20</td>
</tr>
<tr>
<td>-0.5</td>
<td>45</td>
<td>185 ± 20</td>
</tr>
<tr>
<td>0</td>
<td>45</td>
<td>185 ± 20</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>period:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial</td>
<td>45</td>
<td>177 ± 21</td>
</tr>
<tr>
<td>before 50 mg</td>
<td>45</td>
<td>174 ± 24</td>
</tr>
<tr>
<td>before 100 mg</td>
<td>45</td>
<td>173 ± 18</td>
</tr>
<tr>
<td>before 200 mg</td>
<td>45</td>
<td>173 ± 16</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 2. Blood Pressure Levels (M ± SD) after 2 Months of Spironolactone Treatment

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>n</th>
<th>SBP</th>
<th>DBP</th>
<th>Upright SBP</th>
<th>Upright DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>45</td>
<td>161 ± 18</td>
<td>104 ± 10</td>
<td>156 ± 20</td>
<td>105 ± 11</td>
</tr>
<tr>
<td>100</td>
<td>45</td>
<td>157 ± 17</td>
<td>102 ± 10</td>
<td>155 ± 20</td>
<td>105 ± 10</td>
</tr>
<tr>
<td>200</td>
<td>45</td>
<td>155 ± 23</td>
<td>99 ± 10</td>
<td>148 ± 24</td>
<td>103 ± 10</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 3. Number and Per Cent of Patients Reaching a Pressure Level Below M ± 1 SD after Spironolactone Treatment for an Age- and Sex-Matched Reference Population from Southern Sweden

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>n</th>
<th>SBP</th>
<th>%</th>
<th>DBP</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>45</td>
<td>22</td>
<td>49</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>100</td>
<td>45</td>
<td>24</td>
<td>53</td>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>200</td>
<td>45</td>
<td>30</td>
<td>67</td>
<td>24</td>
<td>53</td>
</tr>
</tbody>
</table>

X^2-test for trend 1.6 (not significant); p = 2.9 (not significant).

SBP = systolic blood pressure; DBP = diastolic blood pressure.
SPIRONOLACTONE ONCE DAILY IN PRIMARY HYPERTENSION

PRA, the sex distribution, and the mean age were determined for these groups. Subsequently it appeared (table 5) that "good" responders were characterized by higher age and a lower mean PRA value. There was no significant difference in the response between males and females (Fisher's exact test not significant).

The effects of spironolactone on the biochemical parameters are summarized in Table 6. During treatment with spironolactone, serum sodium and magnesium decreased, while potassium, creatinine, urate, and triglycerides increased. However, all changes were within normal ranges. No changes were observed regarding glucose and cholesterol values.

Decreases in serum sodium and magnesium were not dose-dependent whereas increases in serum potassium and creatinine were dose-correlated. Thus, serum potassium concentration was unchanged with 50 mg spironolactone and reached 4.3 ± 0.3 mmoles/liter \( (p < 0.02) \) with 100 mg. Serum creatinine concentration rose to 91.5 ± 19.2 \( (p < 0.02) \) and to 93.8 ± 21.3 \( (p < 0.002) \) mmoles/liter with 50, respectively 100 mg, spironolactone.

As previously mentioned, five patients did not complete the entire investigation due to the following reasons: two women (WHO I) experienced increased menstruation on 100 and 200 mg spironolactone; one man (WHO I) had tachycardia and blurred vision on 50 mg; another man experienced numbness and paresthesias during the first placebo period and never entered active therapy; and another man failed to attend admission to the first active period.

Of the 45 patients who completed the study, the following side effects were recorded: menstrual irregularities in three patients on active therapy; gynecomastia in one patient on 50 mg spironolactone and in one patient on placebo; decreased libido in two patients on 200 mg. General fatigue, lethargy, and headache were reported by several patients during active therapy as well as on placebo.

### Table 4

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>n</th>
<th>ΔMAP (mm Hg)</th>
<th>Coefficient of correlation</th>
<th>Coefficient of variance (RI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>42</td>
<td>18 ± 11</td>
<td>-0.47</td>
<td>0.22</td>
<td>0.002</td>
</tr>
<tr>
<td>100</td>
<td>42</td>
<td>19 ± 13</td>
<td>-0.54</td>
<td>0.29</td>
<td>0.001</td>
</tr>
<tr>
<td>200</td>
<td>42</td>
<td>21 ± 13</td>
<td>-0.58</td>
<td>0.38</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Figure 3. Correlation between supine ΔMAP during spironolactone 200 mg and initial upright PRA.

Table 5. Evaluation of "Good" and "Bad" Responders to Spironolactone Treatment (50, 100, and 200 mg once daily) as Regards to Mean Arterial Pressure (ΔMAP), Sex, and Age

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Dichotomized variable: mean ΔMAP</th>
<th>No. of observations</th>
<th>Cont. dep. variable: mean PRA upright</th>
<th>Point biserial corr. coefficient</th>
<th>Distribution M/F</th>
<th>Fisher exact test M/F</th>
<th>Mean age (yrs)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18</td>
<td>22</td>
<td>26</td>
<td>0.32</td>
<td>-0.40</td>
<td>9/13</td>
<td>ns</td>
<td>55/56</td>
<td>55</td>
</tr>
<tr>
<td>&lt;18</td>
<td>20</td>
<td>8</td>
<td>0.64</td>
<td></td>
<td>14/6</td>
<td>ns</td>
<td>49/46</td>
<td>48</td>
</tr>
<tr>
<td>≥19</td>
<td>23</td>
<td>29</td>
<td>0.33</td>
<td></td>
<td>10/13</td>
<td>ns</td>
<td>53/56</td>
<td>55</td>
</tr>
<tr>
<td>&lt;19</td>
<td>19</td>
<td>8</td>
<td>0.66</td>
<td></td>
<td>13/6</td>
<td>ns</td>
<td>50/46</td>
<td>48</td>
</tr>
<tr>
<td>≥21</td>
<td>21</td>
<td>31</td>
<td>0.31</td>
<td></td>
<td>9/12</td>
<td>ns</td>
<td>51/57</td>
<td>54</td>
</tr>
<tr>
<td>&lt;21</td>
<td>21</td>
<td>11</td>
<td>0.65</td>
<td></td>
<td>14/7</td>
<td>ns</td>
<td>52/46</td>
<td>49</td>
</tr>
</tbody>
</table>

ns = not significant; M = male; F = female; PRA = plasma renin activity.
The present investigation has shown that 50, 100, and 200 mg spironolactone, each dose administered once daily for periods of 2 months, significantly decreased BP. This effect was obtained during all three dose regimens independent of initial BP levels. When comparing the antihypertensive effect of the three dosages, 200 mg was found to be more effective than 50 but not 100 mg of spironolactone. In earlier reported dose-response studies with spironolactone, the drug has been dispensed in divided daily doses ranging from 100 to 400 mg. In these studies it was shown that 100 to 200 mg spironolactone gave a clinically optimal dose-response in comparison with 400 mg with regard to antihypertensive effect and simultaneously recorded frequency of side effects.

Limited data have been published concerning principles of adequate therapeutic response in primary hypertension. It would be logical to take into account not only the BP reduction but also the BP level achieved. However, absolute criterias for what is to be considered "normal" are lacking, and probably only long-term prospective studies in extensive hypertensive patient populations could elucidate this issue satisfactorily. We have used the BP distributions in different age groups for men and women in the population from which our patients originated in order to evaluate the antihypertensive response to therapy. On 200 mg spironolactone, two-thirds of the patients reached a SBP level (mean BP plus 1 sd) similar to that of the age- and sex-matched reference population. As apparent from table 3, about half of our patients reached this level during treatment with 50 or 100 mg. It is noteworthy that there was no significant difference in this respect between the three dosages used. This is an important fact since the severity and incidence of side effects seem to be correlated to the dose level of spironolactone. A recent Scandinavian study comparing single versus divided daily doses of 100 mg spironolactone showed that the single dose administration was as effective as the divided dose regimen.

PRA determinations as a predictive tool for choosing antihypertensive therapy is still under discussion. Therefore, we found it relevant to characterize those patients arbitrarily classified as "good" or "bad" responders to the three dose regimens applying ΔMAP as the criterion for this classification. This profiling showed that "good" responders were characterized by high-age and low mean PRA values irrespective of sex. It should be noted that the ΔMAP in the "good" responder groups was three times higher than for the respective "bad" responder groups and that this comprised all three dose regimens (table 4 and 5). These findings indicate a certain predictive value of renin profiling regarding the therapeutic response to spironolactone. It seems unlikely that "good" and "bad" responders were related to the degree of bioavailability of the drug in a predominant fashion since the bioavailability of spironolactone/canrenone is not subject to major interindividual variations.

Our patients with primary hypertension had a slight but significant non-dose-dependent decrease in serum sodium and a small but significant dose-dependent increase in serum potassium (0.1 to 0.4 mmole/liter) similar to other observations.

We found a significant decrease in serum magnesium. Surprisingly little attention has been paid to this cation in therapeutics. Thiazides and furosemide increase renal magnesium clearance, but this has not been established for spironolactone. In primary aldosteronism and in secondary aldosteronism, spironolactone has been shown to inhibit the increased renal excretion of magnesium. On this basis our findings are controversial. However, clinical manifestations of magnesium depletion such as paresthesia or muscular cramps were not recorded, and no serum magnesium values below 0.5 mmole/liter were observed. The significant decrease of serum magnesium may make routine measure-
ments worthwhile since the concomitant rise in serum potassium may mask symptoms of magnesium depletion, especially in digitalized patients.\(^8\)

In recent years there has been a renewed interest in the metabolic changes induced by diuretics.\(^9\) Our results regarding the effects on triglycerides and uric acid levels (approximately 10% increase) are in contrast to those of Mertz\(^,\) who did not find elevations of these parameters. Crane and Harris\(^4\) reported an increase of urate values in isolated patients on spironolactone, but there was no increase in the mean levels in patients with primary aldosteronism or in other hypertensive patients.

The fasting blood glucose values were not changed during treatment with the three spironolactone regimens in our study, and to our knowledge glycemic changes have not hitherto been reported. The obvious difference between the effect on glucose tolerance of thiadiazide diuretics (saluretics) and the lack of such by spironolactone may probably find its explanation in these drugs' different actions on serum potassium.

Hyperuricemia and glucose intolerance have been reported to correlate well with serum triglyceride levels\(^7\) but the interrelationships of these factors in hypertension are still to be clarified. It has been a long established fact that uric acid is elevated during thiadiazide treatment,\(^8\) and during recent years it has been found that diuretics increased serum lipid levels.\(^7\) The magnitude of the increase in serum lipids has raised doubts that hemoconcentration alone can fully account for this finding.\(^5\) In our study, no rise in cholesterole levels was found; thus, there was no correlation between triglyceride and cholesterol levels from the individual patients' pretreatment values, which contradicts the hemoconcentration theory. It has been postulated that the elevation of triglycerides may be due to a fall in BP and not directly related to the therapeutic agents applied.\(^3\)

Studies in hypertensive patients have demonstrated a disproportionate reduction in renal blood flow relative to glomerular filtration rate.\(^5\) The superimposition of diuretic therapy with spironolactone may elicit additional decreases in cortical blood flow, thereby affecting the amount of urate coming into contact with tubular sites in the renal cortex that are responsible for urate excretion.\(^9\) We found a small but significant increase in creatinine values which may be consistent with such a hypothesis. Additional studies would be necessary to elucidate the mechanisms responsible for the spironolactone-induced alterations in lipid and urate metabolisms.

In the present investigation five subjects experienced menstrual dysfunction, two had decreased libido, and one developed gynecomastia on active treatment. Consequently, the predominant adverse reactions to drug therapy were caused by intrinsic pharmacological properties of this progestosterone-like steroid. The endocrine effects seemed related to the dose, as previously reported.\(^4,\)\(^6\) However, only two patients were withdrawn from this study due to side effects.

Patient compliance to drug therapy may be improved by once daily dose regimens.\(^4\) Because of its long biological half-life (t\(^1/2\) = 16.8 hours), there is also a pharmacokinetic rationale for giving spironolactone once daily.\(^4\) The absence of gastrointestinal complaints encountered may be ascribed to the once daily regimen administered concomitantly with food intake in the morning.

Acknowledgement

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