Effect of Valsartan and Atenolol on Sexual Behavior in Hypertensive Postmenopausal Women

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Background: The aim of this study was to evaluate the effect of valsartan compared with atenolol on sexual behavior in hypertensive postmenopausal women.

Methods: A total of 120 postmenopausal women, aged 51 to 55 years, with mild to moderate hypertension (diastolic blood pressure [DBP] ≥95 and ≤105 mm Hg) were enrolled. After a 4-week placebo period they were randomized to treatment with valsartan 80 mg ($n = 60$) or atenolol 50 mg ($n = 60$) once daily for 16 weeks, according to a parallel arm design. After 4 weeks of treatment the nonresponder patients (DBP >90 mm Hg) were given a double dose of each drug. Patients were checked at the end of the placebo period and every 4 weeks thereafter. At each visit, sitting blood pressure (BP) was measured by mercury sphygmomanometer (Korotkoff I and V). At baseline and after 16 weeks of treatment, patients were given a questionnaire that comprised 10 self-evaluations of various aspects of sexual desire, orgasmic response, and coital activity. The questions were presented in the form of a visual analog scale.

Results: Both drugs significantly lowered BP without any difference between the two treatments. In the valsartan-treated women, the scores for three of the items related to libido significantly improved: sexual desire (+38%, $P < .01$), changes in behavior (+45%, $P < .001$), and sexual fantasies (+51%, $P < .001$) In contrast, in the atenolol-treated group the scores for the items "sexual desire" and "sexual fantasies" significantly worsened (−18%, $P < .01$ and –23%, $P < .001$, respectively).

Conclusions: These results suggest that in postmenopausal, sexually active hypertensive women, valsartan treatment improved sexual function at least in some respects, whereas atenolol worsened it. This may be relevant for quality of life in these patients and their compliance with antihypertensive therapy. Am J Hypertens 2004;17: 77–81 © 2004 American Journal of Hypertension, Ltd.

Key Words: Valsartan, atenolol, hypertension, women, sexuality.

Most studies about the effects of hypertension and its pharmacotherapy on sexual function have been conducted in men,[1–3] although this topic remains substantially unexplored in women.[4–6] This may in part be due to the difficulty in defining and assessing objective parameters of sexual functioning in women, but even more to the lack of specific questioning about sexual history in female participants to pharmacotherapeutic trials, infrequent involvement of women only, and relatively few female investigators in these trials.[5–8]

Sexual dysfunction in women may manifest as orgasmic impairment, vaginal lubrication failure, vaginismus, loss of libido, or infertility.[4] Little is known about the frequency of these problems among women in the general population[9,10] and much less in both treated and untreated hypertensive women.[4–6,8,11–14]

Drug-induced sexual dysfunction is well known to occur with antihypertensive drugs in men and to exacerbate sexual problems often associated with hypertension per se.[1–3,15] There is evidence, however, that some classes of antihypertensive drugs such as diuretics, central α-agonist and β-blockers have a greter impact on male sexual function than other classes such as calcium antagonists and angiotensin-converting enzyme inhibitors.[2,3,8,11,15–17] Present knowledge about the effects of angiotensin II (Ang II) antagonists is limited, but some data suggest that sexual function in men receiving these agents not only is not altered but even improves.[18–20] There are much fewer data

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on the effects of antihypertensive drugs on female sexual function.[4,6,11–14] Current evidence suggests that clonidine, methyldopa, guanetidine, and reserpine are associated with adverse effects on sexual function (loss of libido, inability to achieve orgasm). β-blockers have been reported to reduce libido, whereas thiazide diuretics may be associated with the worsening of sexual problems (reduced libido and vaginal lubrication), which, interestingly, appear to be ameliorated by weight reduction.[11] Present knowledge on the effects of vasodilators is limited but the Treatment of Mild Hypertensive Study (TOMHS) suggested a higher rate of decreased frequency of sexual activity among women randomized to amlodipine compared with other drugs (acebutolol, enalapril, chlorthalidone, and doxazosin).[14] In a recent case-control study that examined sexual functioning in hypertensive and normotensive women as well as the effects of four major drug classes (diuretics, β-blockers, calcium antagonists, and angiotensin-converting enzyme inibitors), decreased vaginal lubrication, less frequent orgasm, and more frequent coital pain were reported in hypertensive women but no significant difference in the quality of sexual functioning between the different treatment groups was found.[6] To our knowledge, no data are available about the effects of Ang II antagonist on female sexual function.

With this background, the present study aimed to compare the effects on sexual behavior of treatment with the Ang II AT_1-receptor antagonist valsartan and the β_1-selective β-blocker atenolol in hypertensive postmenopausal, sexually active women who were homogeneous for age range, marital/partner status, and use of hormone replacement therapy (HRT) (which allowed us to limit possible dispersion and variability of results due to reduced levels of female sex hormones).

Patients and Methods

The study population included 120 postmenopausal women, aged 51 to 55 years, with a newly diagnosed, previously untreated, mild to moderate essential hypertension (diastolic blood pressure [DBP] >90 and ≤105 mm Hg, systolic BP [SBP] >140 and <180 mm Hg). Menopausal status was defined as the cessation of menses for at least 1 year and was confirmed by plasma follicle-stimulating hormone levels >20 U/L, higher concentrations of follicle-stimulating hormone than luteinizing hormone, and plasma 17-β-estradiol levels <50 pmol/L. All women had been taking HRT for at least 6 months and were still sexually active. This point was investigated through two specific questions, which were part of a series of anamnestic questions: 1) Do you currently have a sex partner, and 2) have you been sexually active during the past month? Only those women who answered "yes" to both these questions were admitted to the study. Patients with diabetes mellitus, obesity (body mass index ≥30), smoking habit, history of breast cancer or thromboembolic diseases, major cardiovascular disease, or noncardiovascular disease or a condition requiring any other concomitant medication were excluded from the study.

The study protocol was approved by the local Ethical Committee and all patients gave their informed consent before enrollment. After a 4-week run-in period on placebo, the patients were randomized to receive valsartan 80 mg once daily or atenolol 50 mg once daily for 16 weeks according to a parallel-arm design. A dose titration was performed after 4 weeks of treatment: the nonresponder patients (DBP >90 mm Hg) were given a double dose of each drug. Patients were checked at the screening visit (baseline), at the end of the placebo period and every 4 weeks thereafter. At each visit BP and heart rate (HR) were evaluated. The BP measurements were obtained from each patient in the seated position by using a standard mercury sphygmomanometer (Korotkoff I and V). At baseline and after 16 weeks of active treatment, patients were given a questionnaire rating the degree of various aspects of the sexual desire[21] with instructions for self-completion. This questionnaire, which was shown to be useful for quantifying sexual desire after menopause,[22] consisted of the following 10 questions: 1) Do you think that your degree of sexual attraction toward your partner has changed; 2) has your sexual interest desire changed at present? 3) has the frequency with which you take initiative in the sexual relation changed; 4) has the frequency with which your partner takes the initiative in the sexual relation changed; 5) has your behavior changed when your partner has asked you for sexual relations; 6) have your sexual fantasies or dreams changed; 7) has sexual excitement changed; 8) has coital activity changed; 9) have the intensity and frequency of your orgasmic response modified; 10) has coital difficulty or pain changed? The questions were presented in the form of a visual analog scale (VAS). The patients could answer choosing from seven options that ranged from "worsened a lot" to "improved a lot." To present the results in a clear form, numeric values were allocated to the patients' answers; consequently "no change" is rated as 0, "worsened a lot" is given the lowest rating of −3, and "improved a lot" is given the highest rating of +3. After assurance of confidentiality, questionnaires coded using identification numbers were completed by the respondent in a private area and responses were returned in a sealed envelope. The questionnaire administered in the first visit actually compared the results with the patient's sexual behavior before menopause, whereas the questionnaire administered after 16 weeks of antihypertensive treatment compared the results with those recorded at the baseline visit.

Statistical Analysis

Data are given as mean ± SD. To make the VAS data more comparable, they were all changed into positive values assigning a value of 0 to the score –3 and a value of 6 to the score +3. Statistical analysis of the data was performed by analysis of variance, and considered only

Table 1. Baseline demographic and clinical characteristics of postmenopausal hypertensive women in the two treatment groups

	Valsartan (n = 60)	Atenolol (n = 60)
Age (y)	53.4 ± 1.1	53.3 ± 1.0
Hypertension duration (y)	1.9 ± 0.6	2.1 ± 0.7
Menopause duration (y)	2.1 ± 0.5	2.0 ± 0.4
HRT duration (y)	1.1 ± 0.2	1.0 ± 0.2
BMI (kg/m^2)	25.6 ± 2.0	25.5 ± 1.9
SBP (mm Hg)	158.6 ± 10.1	159 ± 10.5
DBP (mm Hg)	99.2 ± 4.6	99.8 ± 4.8
HR (beats/min)	75.5 ± 8.3	76.1 ± 8.0

BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; HRT = hormone replacement therapy; SBP = systolic blood pressure.

those patients who completed the trial and who completed the questionnaire fully and correctly (104 patients). The homogeneity of pretreatment values of BP was evaluated by χ^2 test. The differences between the two groups were compared using the Student t test for quantitative variables and nonparametric tests (signed rank test and Wilcoxon two-sample test) for the other variables. A value of $P <$ .05 was considered to be significant.

Results

A total of 120 women (mean age 53.4 years) entered the study and 104 completed it (50 in the atenolol group and 54 in the valsartan group). Five patients were lost to follow-up. Four patients interrupted the trial because of side effects (three in the atenolol group [one for hypotension, one for bradycardia, and one for fatigue and cold extremities] and one in the valsartan group [for headache and dizziness]). Nine patients failed to complete the questionnaire fully and correctly.

Table 1 shows the baseline clinic and demographic characteristics of the patients in the two study groups. No significant difference was found in the parameters examined.

Valsartan and atenolol similarly lowered BP levels, with no significant difference between treatments. The SBP and DBP mean decreases were already significant after 4 weeks of treatment with both valsartan (−10. 9/9. 7 mm Hg, $P <$ .01 v baseline) and atenolol (−12/11.4 mm Hg, $P <$ .01 v baseline), were more marked after dose titration (−18/15.2 mm Hg with valsartan $P <$ .001 and −19.5/15. 7 mm Hg with atenolol $P <$ .001) and persisted after 16 weeks of treatment (−19.6/15.7 mm Hg and −19.1/15.3 mm Hg, respectively). Heart rate significantly slowed with atenolol (from 76.2 ± 8.3 to 54.2 ± 2.8 beats/min, $P <$ .0001 v baseline), whereas it did not change with valsartan.

Dose doubling was necessary in 31 of 54 patients treated with valsartan and in 25 of 50 patients treated with atenolol. Normalization of BP (DBP <90 mm Hg) was achieved by 62% of the valsartan-treated patients and by 58% of the atenolol-treated patients.

The differences in sexual behavior observed with the VAS based questionnaire after 16 weeks of therapy in the two treatment groups are shown in Fig. 1.

Valsartan-treated women showed significantly increased scores for items relating to question 2 ("Has your sexual interest/desire changed at present?") (from 2.09 ± 0. 68 to 2.89 ± 0. 81, +38%, $P <$ .01 v baseline), question 5 ("Has your behavior changed when your partner has asked you for sexual relations?") (from 2.36 ± 0.86 to 3.42 ± 1.25, +45%, $P <$ .001 v baseline), and question 6 ("Have your sexual fantasies or dreams changed?") (from 2.23 ± 0.78 to 3.40 ± 1.26, + 51%, $P <$ .001 v baseline). Scores for items relating to the other questions did not register statistically significant differences from baseline.

By contrast, sexual functioning appeared to be worsened by treatment with atenolol. The items showing greater deterioration in scores correspond to question 2 (from 2.17 ± 0.71 to 1.78 ± 0.89, −18%, $P <$ .01 v baseline and $P <$ .05 v valsartan) and question 6 (from 2.33 ± 0.65 to 1.79 ± 0.93, −23%, $P <$ .001 v baseline and $P <$ .001 v valsartan). In addition the score for question 5 was significantly lower in the women treated with atenolol than in those given valsartan (2.39 ± 0.90 v 3.42 ± 1.25, $P <$ .001). Scores for the other questions remained substantially unchanged from baseline.

Discussion

The results of the present study indicated that despite similar antihypertensive efficacy, the Ang II AT_1 receptor antagonist valsartan and the β-adrenergic blocker atenolol displayed dissimilar effects on sex behavior in hypertensive postmenopausal women.

During valsartan treatment, women's sexual functioning not only did not change but even improved: the patients' subjective perception of some dimension of libido such as sexual desire, sexual fantasies, and behavior when the partner asked for sexual relations improved significantly after 16 weeks of therapy. By contrast, atenolol treatment seemed to produce a worsening of sexual functioning by significantly reducing the score for two items related to libido (sexual desire and sexual fantasies) and also being significantly different from valsartan in the effect on women's behavior in response to partner initiative.

Reasons for such a different influence of the two drugs on female sex behavior are unclear. One possible explanation might be their different effect on plasma testosterone. Unlike valsartan, which does not seem to affect testosterone levels,[20] atenolol has been demonstrated to reduce plasma testosterone values.[20,23,24] A considerable

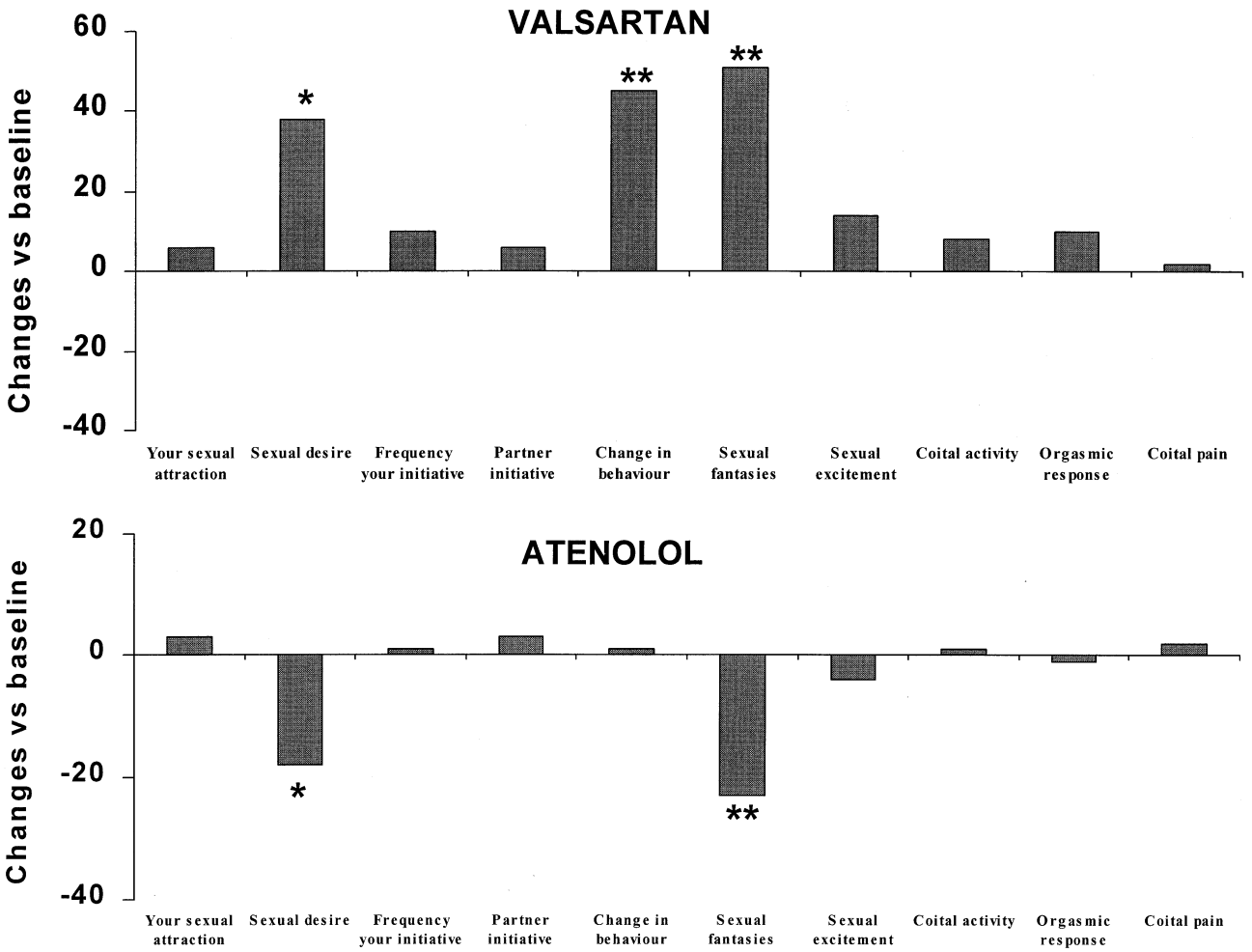

FIG. 1. Differences (%) in the studied aspects of sexual behavior after 16 weeks of treatment with valsartan or with atenolol. *$P < .01$; **$P < .001$ versus baseline.

body of evidence is available on the effects of testosterone in increasing sexual desire both in men and in women[25] and, in menopausal women receiving adequate estrogen through HRT, decreased sexual desire and activity had been related to androgen insufficiency.[26,27] Therefore, possible further reduction in testosterone levels induced by atenolol treatment might be responsible for the observed decrease in libido in our study.

Because female sexual functioning is influenced also by the physical and emotional well-being of the individual,[28] the improvement in sexual behavior observed with valsartan might also be related at least in part to the general improvement in the quality of life indices reported with Ang II antagonists.

As no difference was observed between the two treatments with regard to BP control, we can exclude the possibility that the observed difference in the effect on sexual behavior was due to a different BP lowering effect of valsartan and atenolol.

In conclusion, the results of the present study, which refer to a fairly homogeneous sample of postmenopausal hypertensive women, indicate that the Ang II antagonist valsartan and the β-blocker atenolol exert different influence on female sex behavior and that, despite similar antihypertensive efficacy, valsartan may offer some advantage in terms of quality of sexual life and compliance with antihypertensive treatment.

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