Bisoprolol and Hypertension: Effects on Sexual Functioning in Men

C. P. MATTHIJS BROEKMAN, STEFAN M. HAENSEL, LOUIS L. M. VAN DE VEN, and A. KOOS SLOB

Objectives - To investigate prospectively the effects of the selective B_1 adrenoceptor blocker bisoprolol on sexuality of men with hypertension.

Design - In newly diagnosed patients (group I): double-blind, crossover, placebo controlled. In men with hypertension on antihypertensive treatment (group II): crossover design.

Setting - Large area in and around Rotterdam, The Netherlands.

Patients - Twenty-six men (criteria: between 25 and 70; no disease etc known to affect sexual functioning) were recruited through their general practitioners. Group I (n = 13) fulfilled the selection criteria, sitting blood pressure systolic ≥ 160 mm Hg and/or diastolic ≥ 95 mm Hg, measured on 3 different days. Group II (n = 13) patients already on antihypertensive treatment.

Main outcome measures - Data on blood pressure. Qualitative and quantitative data on sexuality through questionnaires, including personal and sexual history, sexual functioning, sexual satisfaction and erectile difficulties.

Results - Bisoprolol is an effective antihypertensive drug with no detrimental effects on sexuality in newly diagnosed men with hypertension. In men already on antihypertensive medication bisoprolol improved sexuality in some parameters, i.e. firmness of erection during coitus, contentedness with sexual functioning and satisfaction with own sexuality.

Conclusion - Bisoprolol is an effective antihypertensive agent with no sexual side effects.

C. P. Matthijs Broekman, Stefan M. Haensel, and A. Koos Slob are at the Department of Endocrinology and Reproduction, Faculty of Medicine and Health Sciences, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands. Louis L. M. Van de Ven is at E. Merck Ned. Inc., Pharma Division, P.O. Box 8198, 1005 AD Amsterdam, The Netherlands.

The authors would like to express their appreciation to Professor D. L. Rowland for statistical advice, to F. H. Jonker for assistance in collecting the data, and to Professor J. J. van der Werff ten Bosch for critical reading of an earlier version of the manuscript.

Address correspondence to Professor A. K. Slob at the above address.

Sexual dysfunction is a relatively common complication of hypertension and antihypertensive drug therapy in male patients.[1-3] Sexual function in hypertensive women, although not frequently investigated, does not seem to be adversively affected by medication.[3,4] In male patients, the severity of sexual dysfunctioning seems to depend on the type of drug or the therapeutic regimens used.[5] The incidence of erection problems (i.e., impotence) with B_1 blocking agents, frequently first choice treatment of hypertension, varies between 5% and 43% in several studies.[1,6] The underlying pathophysiological mechanism may consist of a combination of central and peripheral vascular effects.

Although there is no doubt about the occurrence of sexual problems in men with antihypertensive treatment, detailed information about their sexuality, in general, and their sexual dysfunction(s) or difficulties, in particular, is usually lacking. More detailed studies into the effects of antihypertensive drugs on sexual functioning are therefore needed. Or, as Bansal[1] wrote, "There is a great need for research in the area of sexual function and hypotensive therapy. . . . Sexual functioning should be thoroughly evaluated. . . . Drug studies should be prospective, double-blind, and preferably crossover and have placebo controls" (p. 9).

Bisoprolol is a relatively new, highly selective B_1-receptor blocker with presumably no effects on peripheral circulation.[7] Although not systematically studied, no severe sexual side effects and a low incidence of "impotence" were encountered in postmarketing surveillance studies.[8]

The present study was undertaken to investigate prospectively in detail the effects of bisoprolol on sexuality in men with hypertension. Two groups were studied: men with newly diagnosed hypertension (group 1) and men already on antihypertensive medication (group 2).

PATIENTS AND METHODS

Twenty-six men with hypertension were recruited through their general practitioners. After full discussion of the aims and procedures of the study, all patients gave informed consent to participate in the study. The study was approved by the ethical committee of the academic hospital Dijkzigt in Rotterdam. The patients fulfilled the following criteria: ages between 25 and 70; no concommitant disease, former surgery, or the use of drugs (other than antihypertensive drugs) known to affect sexual functioning. Two groups were formed: Group 1—men ($N = 13$) with recently discovered hypertension, measured on three consecutive independent occasions (sitting blood pressure systolic $\geq$ 160 mm Hg and/or diastolic $\geq$ 95 mm Hg); Group II—men ($N = 13$) with known hypertension currently on antihypertensive medication.

Men in Group 1 were randomly exposed to a double-blind crossover experimental design, two 6-week periods. Seven started on placebo followed by bisoprolol treatment (5mg/day); six had bisoprolol first followed by placebo. Men in Group 2 were exposed to a crossover design, also

two 6-week blocks; seven started with bisoprolol followed by their own medication; six continued with their own medication for 6 weeks followed by bisoprolol treatment. No interim washout periods were included because the 6-week blocks were thought to be adequate to rule out a carry-over effect.

Following a 5-minute rest, sitting pulse rate and blood pressure were determined by the general practitioner at the start of the study, at the second visit (after 6 weeks) and at the third visit (after 12 weeks).

Sexual information was gathered through questionnaires that included items on personal and sexual history, sexual functioning, sexual satisfaction, and erectile difficulties. The questionnaires are frequently used in our studies[9] and are translated from those used in the psychosexual laboratory of Julian Davidson, Stanford University, USA. The response forms were completed three times: at the start of the study, after 6 weeks, and after 12 weeks. The questionnaires comprised open questions, multiple choice questions, seven-point semantic scales, and visual 100 mm analog scales.

Heart rate and blood pressure data were subjected to one-way ANOVA for repeated measures.[10] Further analysis was with the LSD-procedure.[11] From the sexuality data, only the second and third questionnaires were compared because it was thought that the first questionnaire data were possibly biased since the patients were not used to answering questions about their sexual functioning (the so-called recall bias[12]). Nevertheless, the first questionnaire data will be presented. The data of Groups 1 and 2 were analysed separately.

RESULTS

Mean ages of the patients in Groups 1 and 2 were identical (51.2 years) with comparable ranges (33–62 and 27–63, respectively). In each group, 12 of the 13 men were married, all men had a sexual relationship with a woman. All men reported high levels of contentedness with their relationship; mean values of 5.9 (Group 1) and 5.8 (Group 2) on a 1 (=low) to 7 (=high) scale. Of the patients in group 2, 5 used atenolol, 3 metoprolol, 3 nifedipin, 1 triamterence, and 1 captopril.

As can be learned from Table 1, bisoprolol was effective in controlling hypertension and heart rate. In the newly diagnosed patients (Group 1) bisoprolol significantly lowered heartrate and systolic/diastolic blood pressure compared to baseline and placebo. For the latter two parameters also, a significant placebo effect was found, namely, lower values compared to onset of study. In the patients of Group 2, bisoprolol was as effective as their original medication in controlling heartrate and hypertension.

Frequencies of sexual functioning are listed in Table 2. In both groups bisoprolol did not significantly alter sexual functioning compared to either placebo (Group 1) or own medication (Group 2). It should be kept in mind, as was explained earlier, that only the data of the second and third questionnaire were statistically compared. In the men of group 2,

TABLE 1

Sitting heart rate (b.p.m.) and blood pressure (mm Hg) of patients with hypertension (mean (SEM)).

	Start study (no treatment[a] or own medication[b])		Placebo[a] or own medication[b]		Bisoprolol	
Group 1 (newly diagnosed) N = 13						
Heartrate	79.8	(4.4)	79.6	(4.3)	65.5	(4.1)[1]
Systolic	170.9	(4.8)	156.0	(5.8)[2,4]	148.0	(4.6)[3]
Diastolic	106.0	(1.3)	96.9	(2.9)[2]	90.1	(2.0)[1]
Group 2 (known hypertension) N = 13						
Heartrate	72.5	(3.1)	72.1	(2.9)	74.0	(2.2)
Systolic	155.5	(4.2)	147.5	(4.4)	148.2	(4.6)
Diastolic	98.2	(1.3)	92.5	(1.7)[4]	95.6	(2.3)

Note: All men were exposed to a cross-over design, i.e., 6 weeks placebo or own medication and 6 weeks bisoprolol treatment. Only statistically significant differences are indicated.
[1] $p<0.01$ from placebo and start study
[2] $p<0.01$ from start study
[3] $p<0.01$ from start study, $p<0.05$ from placebo
[4] $p<0.05$ from start study
[a] Group 1
[b] Group 2

two differences showed a trend toward statistical significance: a rise in frequency of morning erections ($p=.097$) and in the frequency of coitus with orgasm ($p=.075$).

The data regarding the quality of sexual functioning are shown in Table 3. In the males with newly diagnosed hypertension no statistically significant differences between placebo and bisoprolol were found for firmness of erection, duration of erection, sexual desire, contentedness with sexual functioning, and satisfaction with own sexuality. In the group of men with known hypertension, some significant differences emerged between bisoprolol and their own medication. During bisoprolol treatment, higher values were reported for firmness ($F(1,8)=5.58$; $p<0.05$) and duration of erection ($F(1,8)=3.43$; $p=0.10$) during coitus, contentedness with sexual functioning ($F(1,11)=9.63$; $p<0.01$), and satisfaction with sexuality ($F(1,11)=5.06$; $p<0.05$).

DISCUSSION

From the present study it is clear that the B_1 blocking agent bisoprolol is an effective antihypertensive drug with no detrimental effects on sexuality of male patients with hypertension. This was found in newly diagnosed men as well as in men already on antihypertensive medication. In the latter group, even some sexuality parameters improved during bisoprolol treatment compared to their own medication. This could have

TABLE 2

Frequencies (mean/week (SEM)) of sexual functioning of male patients with hypertension.

	Start study (no treatment[a] or own medication[b]		Placebo or own medication[b]		Bisoprolol	
Group 1 (newly diagnosed) N = 13						
Morning erections	2.19	(0.55)	1.92	(0.59)	2.08	(0.42)
Spontaneous erections	1.89	(0.49)	5.39	(2.73)	3.22	(1.19)
Coitus with orgasm	1.42	(0.22)	1.35	(0.21)*	1.46	(0.25)
Sex with partner without orgasm	0.15	(0.08)	0.63	(0.48)*	0.54	(0.37)
Solitary masturbation	0.31	(0.11)	0.44	(0.16)	0.29	(0.11)
Group 2 (known hypertension) (N = 13)						
Morning erections	2.12	(0.52)	1.65	(0.37)	2.96	(0.74)
Spontaneous erections	2.94	(0.98)	2.17	(0.84)	4.55	(1.75)[1]
Coitus with orgasm	1.81	(0.33)	1.31	(0.29)	1.69	(0.33)[1]
Sex with partner without orgasm	0.31	(0.10)	0.15	(0.08)	0.19	(0.09)
Solitary masturbation	0.41	(0.30)	0.38	(0.29)	0.40	(0.29)

Note: All men were exposed to a cross-over design, i.e., 6 weeks placebo or own medication and 6 weeks bisoprolol treatment. Statistical analysis was only performed on last two data points.
*N = 12 (one subject not included: partner pregnant near term)
[1] $p<0.10$
[a] Group 1
[b] Group 2

been a placebo effect. Although carried out in a crossover design fashion, the patients were aware of the drug they were taking. Participation in a study with a "new" drug could make them rate their sexuality more positively. In the newly diagnosed hypertensive men, subjected to a double-blind crossover design, such a phenomenon could not occur. In these patients, no significant differences in any of the sexuality items between bisoprolol and placebo treatment were found. It can be argued that bisoprolol could cause severe sexual difficulties in a small proportion of treated subjects and no difficulty at all in the majority. Inspection of the individual data, however, did not reveal support for this supposition.

Studies on the occurrence of sexual side effects of *selective* B_1 adrenoceptor blockers in hypertensive patients are scarce. There is one case

TABLE 2

Frequencies (mean/week (SEM)) of sexual functioning of male patients with hypertension.

	Start study (no treatment[a] or own medication[b]		Placebo or own medication[b]		Bisoprolol	
Group 1 (newly diagnosed) N = 13						
Morning erections	2.19	(0.55)	1.92	(0.58)	2.08	(0.42)
Spontaneous erections	1.89	(0.49)	5.59	(2.73)	3.22	(1.19)
Coitus with orgasm	1.42	(0.22)	1.33	(0.21)*	1.46	(0.25)
Sex with partner without orgasm	0.15	(0.08)	0.63	(0.48)*	0.54	(0.37)
Solitary masturbation	0.31	(0.11)	0.44	(0.16)	0.29	(0.11)
Group 2 (known hypertension) (N = 13)						
Morning erections	2.12	(0.52)	1.65	(0.57)	2.96	(0.74)
Spontaneous erections	2.94	(0.98)	2.17	(0.84)	4.55	(1.75)[1]
Coitus with orgasm	1.81	(0.53)	1.31	(0.29)	1.69	(0.33)[1]
Sex with partner without orgasm	0.31	(0.10)	0.15	(0.08)	0.19	(0.09)
Solitary masturbation	0.41	(0.30)	0.38	(0.29)	0.40	(0.29)

Note: All men were exposed to a cross-over design, i.e., 6 weeks placebo or own medication and 6 weeks bisoprolol treatment. Statistical analysis was only performed on last two data points.
*N = 12 (one subject not included: partner pregnant near term)
[1] $p<0.10$
[a] Group 1
[b] Group 2

been a placebo effect. Although carried out in a crossover design fashion, the patients were aware of the drug they were taking. Participation in a study with a "new" drug could make them rate their sexuality more positively. In the newly diagnosed hypertensive men, subjected to a double-blind crossover design, such a phenomenon could not occur. In these patients, no significant differences in any of the sexuality items between bisoprolol and placebo treatment were found. It can be argued that bisoprolol could cause severe sexual difficulties in a small proportion of treated subjects and no difficulty at all in the majority. Inspection of the individual data, however, did not reveal support for this supposition.

Studies on the occurrence of sexual side effects of *selective* B_1 adrenoceptor blockers in hypertensive patients are scarce. There is one case

TABLE 3

Quality of sexual functioning during last week of 6-week block (mean (SEM); visual 100 mm analog scale) of male patients with hypertension

	Start study (no treatment or own medication[b])			Placebo[a] or own medication[b]			Bisoprolol		
	(N)			(N)			(N)		
Group 1 (newly diagnosed)									
Firmness of erection									
during coitus	7	91.4	(2.7)	11	72.1	(7.0)	11	79.3	(7.4)
during masturb	4	86.5	(1.7)	7	73.5	(6.2)	4	83.5	(3.2)
spontaneous	11	50.5	(10.4)	12	62.3	(9.3)	12	67.6	(9.0)
Duration of erection									
during coitus	7	78.4	(7.3)	11	74.8	(5.5)	11	81.2	(6.9)
during masturb	4	73.0	(9.5)	6	77.2	(5.6)	4	79.5	(1.2)
Sexual desire	11	40.4	(8.2)	12	56.2	(5.8)	12	49.5	(8.0)
Contentedness with sexual functioning	10	62.1	(10.3)	12	69.9	(6.8)	12	70.5	(8.0)
Satisfaction with own sexuality[a]	13	4.5	(0.3)	13	4.8	(0.3)	13	5.0	(0.3)
Group 2 (known hypertension)									
Firmness of erection									
during coitus	9	67.1	(10.8)	9	40.4	(12.4)	11	65.7	(8.3)[1]
during masturb	3	42.7	(20.2)	3	37.7	(15.3)	5	67.0	(15.5)
spontaneous	12	55.8	(8.2)	13	48.0	(7.8)	13	56.5	(8.3)
Duration of erection									
during coitus	9	63.8	(10.8)	9	41.4	(12.5)	11	51.6	(10.6)[2]
during masturb	2	56.0	(22.6)	2	49.5	(19.4)	3	64.0	(14.3)
Sexual desire	13	50.8	(7.0)	13	43.7	(6.6)	13	45.2	(6.6)
Contentedness with sexual functioning	13	61.1	(9.2)	12	47.8	(9.6)	13	61.0	(9.4)[3]
Satisfaction with onw sexuality[a]	13	4.2	(0.5)	13	4.2	(0.4)	13	4.9	(0.4)

Note: All men were exposed to a cross-over design, i.e., 6 weeks placebo or own medication and 6 weeks bisoprolol treatment. Statistical analysis were performed only on last two data points.

[1] $p<0.05$
[2] $p<0.10$
[3] $p<0.01$
[a] scored on a semantic scale (1 = low, 7 = high)
[a] Group 1
[b] Group 2

report about a change of treatment from propanolol to atenolol, which made the male patient regain normal sexual function.[13] There is one study in normotensive men of one-week treatment with each of four beta-blockers (atenolol, metopropol, pindolol propranolol) which yielded inconclusive results on sexual functioning.[14] In the latter study, however, it was suggested that some men may be especially vulnerable to

sexual dysfunction in association with propanolol. This drug, a well-known nonselective beta-blocker, is notorious for its sexual side effects.[5,6,15–17]

From the present study, it seems warranted to say that bisoprolol is an effective antihypertensive drug with no sexual side effects. It seems possible that men on antihypertensive medication who already have erectile difficulties might benefit from bisoprolol treatment. Finally, it should be kept in mind that from this study, no conclusions can be drawn about the long-term effects of bisoprolol on sexual functioning.

REFERENCES

1. Bansal S: Sexual dysfunction in hypertensive men. A critical review of the literature. *Hypertension 12*:1–10, 1988.
2. Hirshkowitz M, Karacan I, Gurakar A, Wiliams RL: Hypertension, erectile dysfunction, and occult sleep apnea. *Sleep 12*:223–232, 1989.
3. Bulpitt CJ, Beevers DG, Butler A, et al: The effects of anti-hypertension drugs on sexual function in men and women: A report from the DHSS hypertension care computing project (DHCCP). *J Hum Hypert 3*:53–56, 1989.
4. Riley AJ, Steiner JA, Cooper R, McPherson CK: The prevalence of sexual dysfunction in male and female hypertensive patients. *Sex marital Ther 2*:131–138, 1987.
5. Bulpitt CJ, Dollery CT: Side effects of hypotensive agents evaluated by a self-administered questionnaire. *Br Med J 3*:485–490, 1973.
6. Smith PJ, Talbert RL: Sexual dysfunction with antihypertensive and antipsychotic agents. *Clin Pharm 5*:373–384, 1986.
7. Leopold G, Ungethum W, Pabst J, Simane Z, Buhrung KU, Wiemann H: Pharmacodynamic profile of bisoprolol: a new B_1-selective adrenorecepter antagonist. *Br J Clin Pharmac 22*:293–300, 1986.
8. Van de Ven L, Crama J, De Vries RJ: The postmarketing surveillance of bisoprolol (Emcor®). *TGO/JDR 10*:285–289, 1990.
9. Slob AK, Blom JHM, Van der Werff ten Bosch JJ: Erection problems in medical practice: Differential diagnosis with relatively simple method. *J Urol 143*:46–50, 1990.
10. Perlman G: *The UNIX/STAT handbook: Data analysis programs on UNIX and MSDOS*. Tyngsboro, Wang Inst., 1986.
11. Kirk RE: *Experimental design: Procedures for the behavioral sciences*. Belmont, CA, Brooks/Cole, 1968.
12. Hennekens CH, Buring JE: *Epidemiology in medicine. Boston, Little, Brown, 1987.*
13. *Bathen J: Propranolol erectile dysfunction relieved. Ann Int Med 88*:716–717, 1978.
14. Rosen RC, Kostis JB, Jekelis AW: Beta-blocker effects on sexual function in normal males. *Arch Sex Behav 17*:241–255, 1988.
15. Greenerg G: Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet 2*:539–543, 1981.
16. Stevenson JC, Umstead GS: Sexual dysfunction due to antihypertensive agents. *Drug Intell Clin Pharm 18*:113–121, 1984.
17. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. *N Eng J Med 314*:1657–1664, 1986.