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Pilot Study of the Endothelin-A Receptor Selective Antagonist BMS-193884 for the Treatment of Erectile Dysfunction

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ABSTRACT: Endothelins have been postulated to be important regulators of penile erectile function. The endothelin-A receptor antagonist BMS-193884 was evaluated as a treatment for mild-to-moderate erectile dysfunction in an animal model and in human volunteer subjects. In laboratory studies, organ bath preparations of rabbit and human penile cavernosal tissue strips were incubated with BMS-193884 and exposed to increasing concentrations of endothelins. In rabbit tissue, 1 μM BMS-193884 significantly inhibited contraction to ET-1, ET-2, and ET-3 by 34.5%, 42.9%, and 100%, respectively. In human tissue, 1 μM BMS-193884 inhibited contraction to ET-2 by 44.4%. In rabbit tissue strips contracted with 20 nM of ET-1 or ET-2, BMS-193884 caused dose-dependent relaxation with EC_{50} values of 107.2 ± 32.3 nM and 1.7 ± 0.5 nM, respectively. In anesthetized male rabbits, intravenous administration of BMS-193884 (systemic plasma concentration ≈50 and 100 nM) increased the duration of pelvic nerve-stimulated penile erection. To further assess the safety and efficacy of BMS-193884, 53 men diagnosed with mild-to-moderate erectile dysfunction were administered oral placebo or 100 mg BMS-193884 in a double-blind fashion. Evaluations were based on 1) erectile function testing during 2 in-office visits and 2) diary and questionnaire data of 4 intercourse attempts over 2–4 weeks of home use. Although the drug was well tolerated, BMS-193884 did not significantly improve erectile function during office visits or home use when compared to placebo. Thus, BMS-193884 facilitated cavernosal smooth muscle relaxation ex vivo and prolonged penile tumescence in vivo. In contrast, a pilot clinical study failed to show enhancement of erectile response in men with mild-to-moderate erectile dysfunction. The disparity between the laboratory and clinical studies suggests that there may be differences between species with regard to the role of endothelin in erectile function.

Key words: Corpus cavernosum, erectile function, clinical trial.

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Endothelins (ET-1, ET-2, and ET-3) are a family of potent vasoactive peptides that have important physiologic roles in many tissues. Endothelins have been implicated in various vascular pathological conditions such as Raynaud disease, coronary and cerebral vasospasm, essential pregnancy-induced hypertension, and pulmonary hypertension (Stjernquist, 1998; Turton et al, 1998; Goldie, 1999; Miyauchi and Masaki, 1999). Three receptor subtypes (ET_A, ET_B, and ET_C) bind ET-1, ET-2, and ET-3 with varying specificity and affinity (Ortega Mateo and de Artinano, 1997; Stjernquist, 1998). In blood vessels, smooth muscle cells express ET_A and ET_{B2} receptors that mediate vasoconstriction, whereas endothelial cells express ET_{B1} receptors that mediate vasodilation through the release of nitric oxide and prostaglandins (Ortega Mateo and de Artinano, 1997). Apart from their effects on smooth muscle tone, endothelins also mediate trophic effects, stimulating proliferation and collagen production in vascular smooth muscle cells and fibroblasts (Guarda et al, 1993; Dawes et al, 1996; Rizvi et al, 1996).

In human penile erectile tissue, corpus cavernosum endothelial cells synthesize and release ET-1 (Saenz de Tejada et al, 1991). Radioligand binding experiments indicate that human corpus cavernosum tissue expresses ET_A and ET_B receptors (Saenz de Tejada et al, 1991). In isolated human cavernosal tissue strips, ET-1 elicits a slowly developing contractile response that is long-lasting and appears to be unaffected by age, erectile dysfunction status, or diabetes (Saenz de Tejada et al, 1991; Christ et al, 1995; Kim et al, 1996). Similar to other blood vessels, endothelins may also cause vasodilation in the corpora cavernosa. This is demonstrated by the intravenous infusion of low concentrations of ET-1 (0.1–5 μg/kg body weight) into rats, which induces transient penile erections through a nitric oxide–dependent mechanism (Ari et al, 1996). Stimulation of cultured human corpus cavernosum smooth muscle cells by ET-1 causes calcium to increase in both cytoplasmic and nuclear compartments (Zhao et al, 1995). Elevations in cytoplasmic calcium stimulate contraction in smooth muscle cells, while increases in nuclear and/or cytoplasmic calcium have been associated with alterations in gene expression (Bading et al, 1997;

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Neylon, 1999; Somlyo et al, 1999; van Haasteren et al, 1999). Thus, endothelin is believed to act as a paracrine regulator of penile cavernosal smooth muscle tone and may influence various noncontractile functions in cavernosal smooth muscle cells (Battistini et al, 1993; Giraldi et al, 1998). As suggested by studies in other vascular structures, endothelins may regulate tissue remodeling processes such as smooth muscle proliferation and connective tissue synthesis.

The balance of vasoconstricting and vasorelaxing forces on cavernosal smooth muscle is a critical factor in the regulation of penile erection. In order for tumescence/erection to occur, the tonically contracted cavernosal smooth muscle must relax to allow filling of the lacunar spaces with arterial blood (Andersson and Wagner, 1995). BMS-193884 is a novel ET_A receptor selective antagonist that has been shown to ameliorate the effects of pulmonary hypertension (Miyauchi et al, 2000; Murugesan et al, 2000). Such compounds may have utility in reducing the resting tone of the cavernosal smooth muscle and thereby tilting the balance to favor cavernosal smooth muscle relaxation and erection. A pilot study was designed with 2 specific aims. The first aim was to characterize the effects of BMS-193884 in antagonizing endothelin action in isolated strips of penile corpus cavernosum as well as enhancing nerve-induced penile erection in an in vivo animal model. The second aim was to explore the efficacy, safety, and tolerance of BMS-193884 in treating men diagnosed with mild-to-moderate erectile dysfunction. The potential significance of this research was to assess a new class of oral medications, ET_A receptor selective antagonists, as a treatment for male erectile dysfunction.

Materials and Methods

Laboratory Study

BMS-193884 was obtained from Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ) and all stock solutions were made in 5% $NaHCO_3$. Endothelins 1, 2, and 3 were purchased from Peninsula Laboratories (San Carlos, Calif).

Tissue Procurement—The protocols for the procurement and use of human and rabbit tissue in this study were approved by the Institutional Review Board for Human Studies and the Institutional Animal Care and Use Committee at the Boston University Medical Center. Human and rabbit penile cavernosal tissues were obtained and prepared for organ bath studies, as previously described (Kim et al, 1991).

Organ Bath Studies—Organ bath preparations of human or rabbit cavernosal tissue strips at optimal isometric tension (Kim et al, 1991) were subjected to 1 of 2 protocols. For ET dose responses, tissue strips were maximally contracted with physiological salt solution (PSS) containing 120 mM KCl, washed with regular PSS and treated for 30 minutes with vehicle (control) or 10–1000 nM BMS-193884. After this incubation period, cavernosal strips were exposed to increasing concentrations (0.1 nM–30 μM) of ET-1. Baseline tension was defined as 0% contraction and was determined in the presence of papaverine and nitroprusside, as described below. Data for endothelin dose responses were expressed as a percentage of the contraction induced by PSS containing 120 mM KCl. For BMS-193884 dose responses, tissue strips were contracted with 20 nM ET-1 or ET-2. Tissue strips were then exposed to increasing concentrations (0.1 nM–30 μM) of BMS-193884. At the end of each experiment, all tissue strips were treated with 10 μM papaverine and 10 μM nitroprusside to induce maximal relaxation (100%). The total contractile or relaxatory response was defined as the area between the plotted curves and the origin, over the entire range of drug concentrations tested. The degree of inhibition or enhancement in the dose response was determined from the change in total contraction or relaxation, relative to control. EC_{50} values were calculated using Prism software (GraphPad, San Diego, Calif).

In Vivo Pelvic Nerve Stimulation Studies—Adult male New Zealand White rabbits (3.0–3.5 kg) were sedated with an intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg). Anesthesia was maintained with 0.2 mL intravenous bolus injections of pentobarbital (25 mg/mL) as needed. A 20-gauge angiocatheter was placed into the carotid artery for on-line measurement of systemic arterial pressure. A 23-gauge minicatheter was inserted into one cavernosal body of the penis for measurement of intracavernosal pressure. Through a midline abdominal incision, the cavernosal branch of the pelvic nerve was isolated on the postero-lateral aspect of the rectum. Electrical stimulation (30 seconds) was achieved with a platinum wire electrode and a square wave generator set at 16 Hz, 10 V, 8 msec pulse duration. Systemic and intracavernosal blood pressures were continuously monitored. Rabbits were subjected to pelvic nerve stimulation 3 minutes after intravenous administration of 1 mL of vehicle or BMS-193884. The systemic plasma concentration of BMS-193884 was estimated to be 50 and 100 nM, assuming a total blood volume of 250 mL in the adult rabbit. All intracavernosal pressure values were expressed as a percentage of mean systemic blood pressure.

Clinical Study

Study Design—This study was approved by the Institutional Review Boards for Human Studies at the Boston University Medical Center and the Robert Wood Johnson Medical School. A double-blind, two-center pilot study was conducted, randomizing 53 men (aged 18–65 years) with at least 6 months duration of erectile dysfunction who were in a heterosexual, monogamous relationship. All signed an informed consent form. The etiology of the erectile dysfunction was assessed using medical history, physical examination, and other diagnostic procedures. Patients were included who had mild-to-moderate erectile dysfunction based on scoring 13–24 on questions 1 through 5 and 15 of the International Index of Erectile Function (IIEF), and who reported that over the last 6 months, they had reduced morning erections, trouble getting erections for intercourse, trouble maintaining erections during intercourse, and were neutral to extremely dissatisfied with their sexual function. Men were excluded if they

Effect of BMS193884 on endothelin-induced contraction

	EC50 (nM)	Total Contractile Response	Percent Inhibition	Number
Rabbit				
ET-1				
Control	27.9 ± 9.4	336.4 ± 34.4	0	6
10 nM BMS193884	29.2 ± 6.1	319.0 ± 28.3	5.2	8
100 nM BMS193884	31.6 ± 7.2	284.4 ± 21.2	15.5	8
1 μM BMS193884	59.2 ± 14.0	220.4 ± 28.9*	34.5	4
ET-2				
Control	59.9 ± 13.5	278.8 ± 12.9	0	4
10 nM BMS193884	44.0 ± 6.8	292.4 ± 20.1	0	4
100 nM BMS193884	83.4 ± 24.5	216.7 ± 31.1	22.3	4
1 μM BMS193884	145.2 ± 47.3	159.1 ± 31.7*	42.9	4
ET-3				
Control	162.4 ± 83.2	74.2 ± 23.5	0	4
10 nM BMS193884	158.1 ± 40.9	47.1 ± 6.7	36.5	4
100 nM BMS193884	. . .	0.8 ± 0.8*	98.9	4
1 μM BMS193884	. . .	0.0 ± 0.0*	100.0	4
Human				
ET-2				
Control	10.9 ± 1.9	445.2 ± 93.1	0	6
10 nM BMS193884	12.5 ± 2.8	408.1 ± 59.8	8.3	6
100 nM BMS193884	34.4 ± 9.7*	330.4 ± 35.3*	25.8	8
1 μM BMS193884	164.2 ± 65.7*	247.8 ± 28.8*	44.4	7

* $P \leq .05$, relative to control.

had endocrinologic erectile dysfunction, radical prostatectomy, significant penile curvature, current or recent gastrointestinal condition, significant coronary artery disease, systolic blood pressure more than 180 or less than 100 mm Hg and diastolic more than 100 or less than 60 mm Hg, any erectile dysfunction treatment prior to and during the study, sexually transmitted diseases, sulfonamide hypersensitivity, or glucose-6-phosphate dehydrogenase deficiency. After initial screening, subjects were asked to perform at least 3 sexual intercourse attempts without taking any study medication and record outcome data on a patient diary and IIEF questionnaire. Subjects subsequently received an in-clinic dose of placebo followed by visual sexual stimulation with or without vibratory stimulation. Outcome efficacy variables included 1) ''angle of erection'' recorded by repeated Polaroid photography in the standing position over a 1-hour observation period and 2) erection grading by patient and study personnel into response (grade 3 or 4 erection) or nonresponse (grade 1 or 2 erection) groups. Grade 1 denoted an increase in penis size without hardness; grade 2, an increase in size with mild hardness insufficient for intercourse; grade 3, an increase in hardness not fully rigid but sufficient for intercourse; and grade 4, a fully rigid erection. After at least a 3-day washout, subjects were randomly assigned to receive either 100 mg of BMS-193884 or an identical-looking placebo in a second in-clinic visit. Similar outcome efficacy variables were determined over a 1-hour observation period. Subjects were then sent home with the study drug or placebo to be taken orally 1–2 hours before attempting sexual intercourse. Diary and questionnaire data were used to assess efficacy of 4 separate attempts at sexual intercourse. Safety assessments were based on all who were dispensed treatment and included data from the above diary and questionnaires as well as adverse event reports, vital signs, electrocardiograms, physical examinations, and laboratory tests.

Results

Laboratory Study

Effect of BMS-193884 on Endothelin-Induced Contraction in Penile Corpus Cavernosum—Incubation of rabbit or human cavernosal tissue strips with BMS-193884 alone did not alter smooth muscle tone. In isolated rabbit cavernosal tissue, 1 μM of BMS-193884 significantly attenuated contraction to ET-1 and ET-2 and increased the mean EC_{50} values by approximately twofold (see the Table). On average, 1 μM of BMS-193884 inhibited contraction to ET-1 and ET-2 by 34.5% and 42.9%, respectively. Lower concentrations of BMS-193884 did not significantly alter the dose response to ET-1 or ET-2 in rabbit cavernosal strips. The contractile response to ET-3 was the least potent in rabbit cavernosal tissue with initial responses occurring at 10–30 nM ET-3. This contraction was completely blocked by 100 nM and 1 μM of BMS-193884. In human cavernosal tissue strips, contraction to ET-2 was progressively attenuated by BMS-193884 in a dose-dependent fashion (Figure 1). On average, 1 μM of BMS-193884 shifted the EC_{50} value from 10.9 nM to 164.2 nM

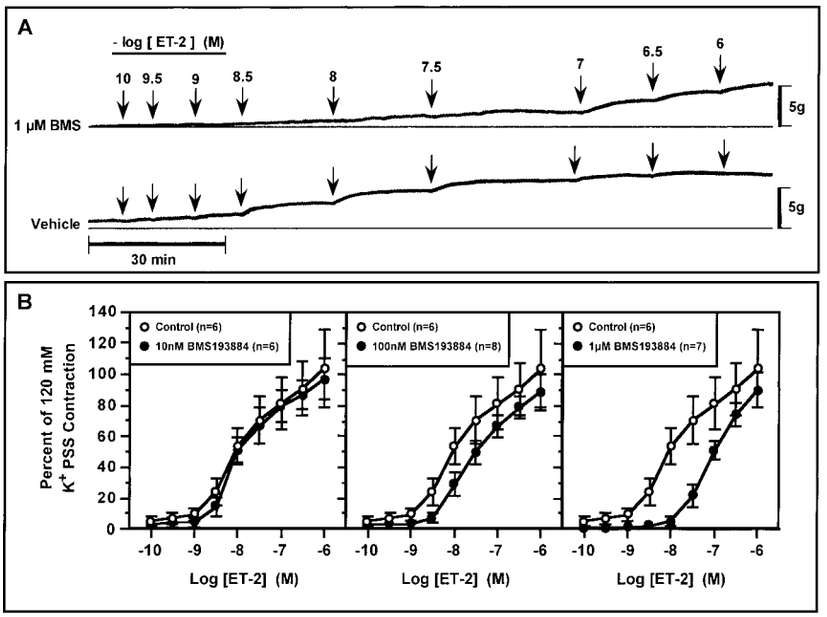

Figure 1. Effect of BMS-193884 on ET-2-induced contraction in human corpus cavernosum. Isolated tissue strips in organ bath preparations were incubated with the indicated concentrations of BMS-193884 or vehicle for 20 minutes and exposed to increasing concentrations of ET-2. Representative organ bath tension recordings are shown in **(A)**. All data were normalized against contractions obtained in the presence of physiological salt solution containing 120 mM K^+ and expressed as mean ± SEM **(B)**. Protocols were repeated in ''n'' different strips of tissue from 3 separate patients.

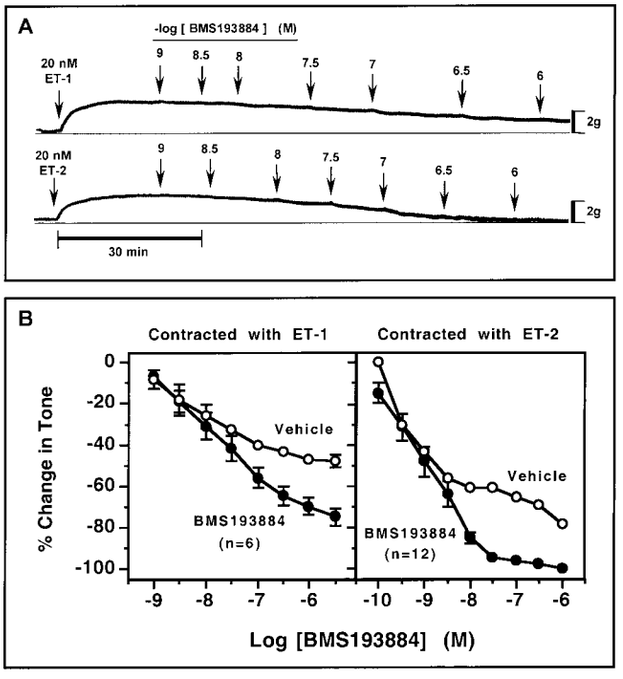

Figure 2. BMS-193884 dose responses. Isolated rabbit cavernosal tissue strips in organ bath preparations were contracted with 20 nM of ET-1 or ET-2 and exposed to increasing concentrations of vehicle (5% $NaHCO_3$) or BMS-193884. Representative organ bath tension recordings are shown in **(A)**. Protocols were repeated in tissue strips from ''n'' different animals and data are the mean ± SEM **(B)**.

and inhibited contraction to ET-2 by 44.4% in human tissue.

BMS-193884 Dose Responses—Submaximal doses (20 nM) of ET-1 and ET-2 caused contractions in rabbit corpus cavernosum strips, which gradually lost tone over 60–90 minutes (the average duration of a dose response). Contraction to ET-1 was more stable than contraction induced by ET-2. BMS-193884 induced relaxation in rabbit cavernosal tissue strips contracted with 20 nM ET-1 or ET-2 with EC_{50} values of 107.2 ± 32.3 nM and 1.7 ± 0.5 nM, respectively. These relaxatory responses were significantly enhanced over the loss in tone observed in tissues receiving only vehicle (Figure 2).

Effect of BMS-193884 on Penile Erection In Vivo—Intravenous administration of BMS-193884 (50 and 100 nM) did not affect systemic arterial blood pressure and did not change the peak intracavernosal pressure caused by nerve stimulation. However, BMS-193884 treatment increased the duration of pelvic nerve-stimulated penile tumescence, as reflected by the prolonged elevation in intracavernosal pressure when compared with controls (Figure 3). The $t_{½}$ values for decay in intracavernosal pressure were estimated to be 34 seconds in control, versus 48 and 69 seconds in animals treated with 50 and 100 nM BMS-193884, respectively.

Clinical Study

There were no significant differences in the BMS-193884 (n = 27) and placebo (n = 26) treated groups in terms

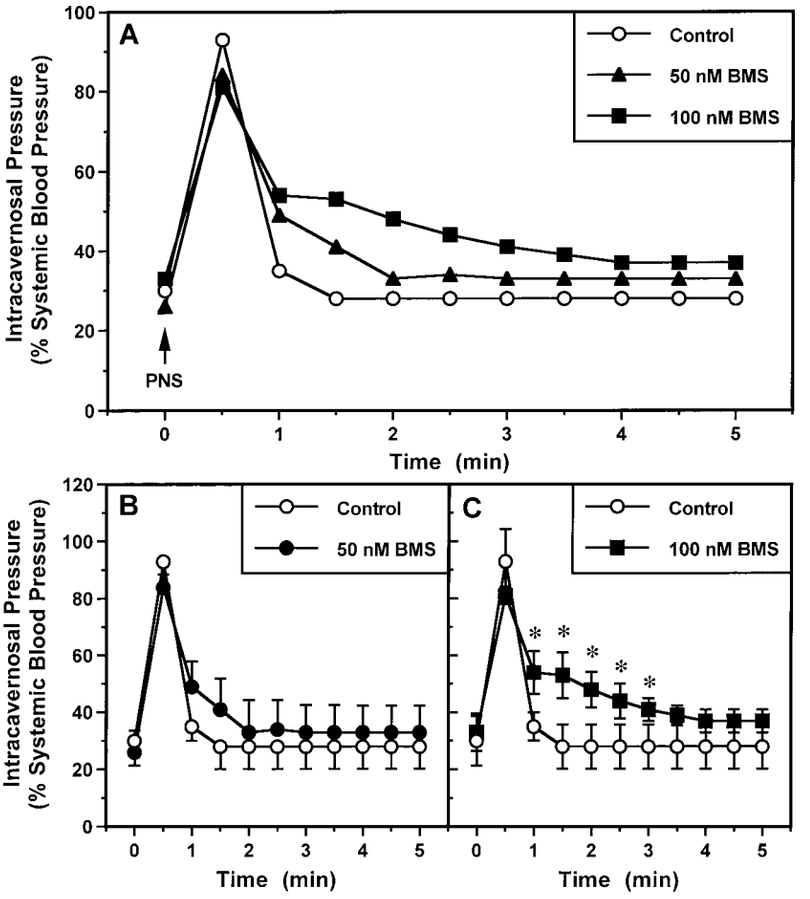

Figure 3. Effect of BMS-193884 on penile erection in the rabbit. Anesthetized male New Zealand White rabbits (3.0–3.5 kg) were administered BMS-193884 by intravenous injection to achieve an estimated systemic plasma concentration of 50–100 nM of drug. Intracavernosal pressure was recorded before, during, and after pelvic nerve stimulation and is expressed as a percentage of the mean systemic blood pressure **(A)**. Each protocol was repeated in 3 separate animals. Mean ± SEM are shown for control and each concentration of BMS-193884 in **(B)** and **(C)** (*$P \leq .05$ compared to control).

of age (54 ± 10.3 vs 55 ± 9.3 years); body mass index (29.4 vs 28.6); and the following sexual function characteristics: 1) the frequency of 1–2 sexual attempts/week (81.5% vs 88.5%), 2) trouble getting and keeping an erection for intercourse (100% vs 100%), 3) somewhat or extremely dissatisfied with sex life (85.2% vs 76.9%), 4) partner somewhat or extremely dissatisfied with sexual relationship (59.3% vs 50%), and 5) less-frequent sexual activity than desired (88.9% vs 84.6%), respectively. A grade 3 or 4 in-clinic investigator-assessed erectile response (the primary efficacy variable) was observed in 5 out of 27 (18.5%) subjects using 100 mg of BMS-193884 compared with 9 out of 26 (34.6%) subjects using placebo. Further, there were no significant differences between treatment groups in the Polaroid-based angle of erection or subject-assessed erectile responses. During home use, there were no significant differences between treatment groups in the patient diary (initiate penetration, intercourse completion, erectile hardness, and intercourse satisfaction). There were also no significant differences in terms of the 5 domain measures of the IIEF responses (Figure 4). There were no deaths and 1 serious adverse event in this study. One subject randomized to placebo was hospitalized due to chest pain. A total of 17 adverse events (12 headaches) were recorded in 14 subjects on BMS-193884 and 2 adverse events in 2 subjects on placebo.

Discussion

The first phase of this pilot study was performed to assess whether BMS-193884 caused diminishment of the contractile response to endothelin in penile corpus cavernosum smooth muscle. The significant but incomplete inhibition of endothelin-induced contraction by BMS-193884 in the organ bath studies is consistent with our previous findings that demonstrated the presence of both ET_A and

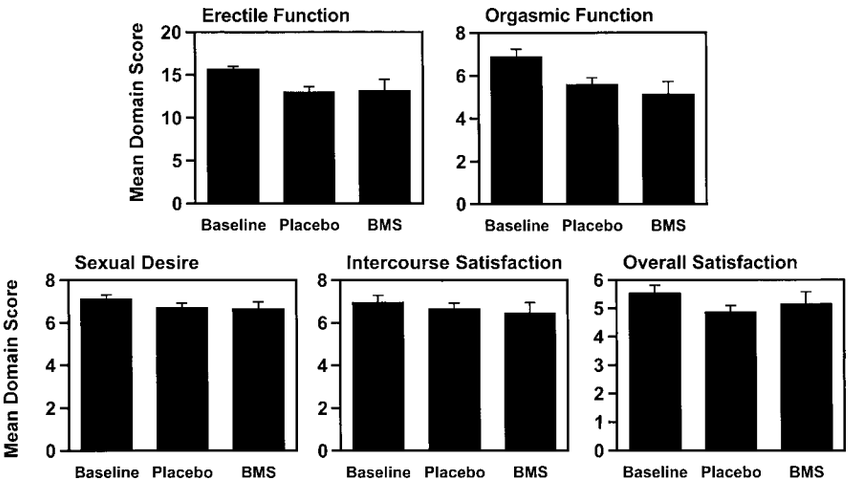

Figure 4. Effect of BMS-193884 on erectile function in patients with mild-to-moderate erectile dysfunction. Shown are the mean scores (± SEM) from the 5 domain measures of the IIEF.

ET_B receptors in penile cavernosal tissue (Saenz de Tejada et al, 1991). Because both receptors can mediate contraction, blocking one subtype does not completely inhibit the response to endothelin. Interestingly, organ bath data from this study indicated that the addition of BMS-193884, subsequent to contraction by endothelin, relaxed cavernosal tissue strips in a dose-dependent manner. Furthermore, our in vivo studies in rabbits demonstrated that acute administration of BMS-193884 prolonged the duration of the nerve-stimulated penile erectile response. These data taken together suggest that BMS-193884 can attenuate the contractile response to endogenous endothelins and effectively prolong erection. These findings are consistent with the hypothesis that endothelin is a local vasoactive modulator in penile corpus cavernosum, which is important for detumescence and maintenance of the flaccid state. However, these observations appear to be inconsistent with the kinetics of interaction between endothelins and their receptors. Because the rate of dissociation between ET-1 and its receptors is extremely slow and ET receptors are internalized upon binding agonist (Traish et al, 1991; Chun et al, 1995; Bremnes et al, 2000), it remains unclear as to how BMS-193884 can antagonize endothelin-induced contraction during a relatively short time scale (less than 10 minutes).

Recent studies on the intracellular trafficking of receptors indicate that both ET_A and ET_B receptors are internalized upon binding agonist via a clathrin-dependent mechanism, but each receptor subtype is apparently sorted through different pathways (Chun et al, 1995; Bremnes et al, 2000). It has been suggested that ET_A receptors are recycled back to the cell surface, whereas ET_B receptors are targeted for degradation in lysosomes (Bremnes et al, 2000). In addition, ET-1 remains bound to an internalized receptor and has been postulated to maintain activation of G-proteins in endosomes (Chun et al, 1995). The prolonged contractile response of endothelins may be mediated by this continuous signaling within internalized agonist-receptor-G-protein complexes, by recycling resensitized ET_A receptors, or both (Chun et al, 1995; Bremnes et al, 2000). To antagonize endothelin-induced contraction, BMS-193884 presumably must bind to the unoccupied ET_A receptor on the cell surface and prevent the agonist from binding. The recycling of receptors could produce a subpopulation of free ET_A receptors available to bind the antagonist. It is also possible that the interaction of BMS-193884 with an allosteric site on the ET_A receptor lowers the affinity of endothelin, causing it to dissociate more quickly. Inhibition of endothelin binding through an allosteric mechanism has been reported for salicylates and BQ-123 (Sokolovsky, 1993; Talbodec et al, 2000). Alternatively, BMS-193884 may also act as an agonist to induce relaxation through another unrelated receptor or ion channel protein. Regardless of the mechanism of action, our data suggested that antagonism of ET_A receptor action by BMS-193884 may be an effective means of prolonging penile erection.

Single-dose, repeat-dose, and genetic toxicity studies with BMS-193884 have been conducted in mice, rats, dogs, and monkeys (unpublished observations, Bristol-Myers Squibb Pharmaceutical Research Institute). Three-month toxicology studies in rats and monkeys indicated that BMS-193884 was well tolerated at all doses (3–300 mg/kg per day). Minimal to mild changes were observed at doses greater than or equal to 30 mg/kg in rats with increased liver weights (hepatocellular hypertrophy and smooth endoplasmic reticulum hyperplasia), decreased thymus and body weights, dilatation, and hyaline droplet formation in renal tubules. In monkeys, no gross histopathologic lesions were seen at any dose, but increased

liver weights and elevated levels of serum alkaline phosphatase and alanine aminotransferase at doses greater than or equal to 30 mg/kg suggest a mild effect of BMS-193884 on liver function. Thus, preclinical toxicity studies in animals supported the further evaluation of BMS-193884 in humans. Safety studies in healthy male volunteers revealed that the most common adverse event was headache, which was dose-dependent, and occurred in all subjects at 200 mg of BMS-193884. Other adverse events included chest discomfort, dizziness/light headedness, visual changes, nausea, and liver enzyme elevations.

Based on these data and that of the organ bath and in vivo animal studies, the second phase of the pilot study was performed to assess whether BMS-193884 was safe and effective for the treatment of men with erectile dysfunction. Despite the efficacy of BMS-193884 in laboratory studies, no significant advantage was observed with the active drug when compared to the placebo in the pilot clinical trial. Thus, BMS-193884 was assessed as not having an effect on erectile function as measured in this study design. The disparity in efficacy between the in vivo animal studies and the clinical studies suggests that there may be important differences between species with regard to the role of endothelin and erectile function. Whereas endogenously produced endothelin may contribute significantly to the maintenance of the flaccid state in the rabbit, its primary role in human penile corpus cavernosum may not be as a contractile agent. In the rat, endothelin receptor antagonists do not significantly alter the erectile response despite exhibiting potent contraction to exogenous ET-1 (Dai et al, 2000). Furthermore, no differences in endothelin-induced contraction were observed in penile cavernosal tissue derived from men with normal erectile function vs. diabetic men with erectile dysfunction (Christ et al, 1995). In contrast, elevations in plasma endothelin levels have been documented in men with erectile dysfunction and up-regulation of ET receptors have been noted in penile cavernosal tissue from diabetic rats and rabbits (Bell et al, 1995; Francavilla et al, 1997; Sullivan et al, 1997). Whether any of the patients in our study had alterations in plasma endothelin levels or ET receptors is unknown. Nevertheless, none of the previously reported changes in plasma endothelin and ET receptors have been directly shown to be causative of increased contractility or reduced relaxation of cavernosal smooth muscle. Endothelin may participate in the pathogenesis of these disease states through other mechanisms such as alterations in smooth muscle cell growth and connective tissue production. The relative content of cavernosal smooth muscle and extracellular matrix influences the structural properties of penile erectile tissue (Nehra et al, 1998). Loss of smooth muscle and increased extracellular matrix components have been associated with erectile dysfunction due to venous leakage (Nehra et al, 1996).

Thus, the roles for endothelins in the regulation of corpus cavernosum smooth muscle contractility remain to be fully elucidated. However, the effects of these peptide hormones on the noncontractile functions of smooth muscle cannot be ignored. Endothelin may be more important as a trophic factor regulating tissue remodeling processes in penile corpus cavernosum, while the adrenergic system plays the major role in maintaining flaccidity. Investigation into the trophic effects of endothelins will add further insight into the multiple roles of these peptides in the penis. Such studies may include testing the efficacy of endothelin receptor antagonists in preventing or reversing adverse tissue remodeling processes such as fibrosis.

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