ELSEVIER

COMBINATION THERAPY USING ORAL ALPHA-BLOCKERS AND INTRACAVERNOSAL INJECTION IN MEN WITH ERECTILE DYSFUNCTION

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ABSTRACT

Objectives. Intracavernosal injection with a combination of agents (ie, phentolamine plus papaverine or alprostadil) has been used in an effort to increase efficacy and reduce side effects compared with single agents. The purpose of this pilot study was to determine the potential role of oral alpha-blockers in combination with intracavernosal therapy in men with erectile dysfunction, for whom intracavernosal therapy alone failed.

Methods. Thirty-eight consecutive men with moderate to severe erectile dysfunction on the basis of history and examination and with minimal or no therapeutic response to intracavernosal alprostadil injection therapy were evaluated. All patients received daily doxazosin titrated to 4 mg over 3 weeks in combination with intracavernosal therapy as needed for 12 weeks. Efficacy was assessed at 4, 8, and 12 weeks after doxazosin titration using the 15-item, self-administered International Index of Erectile Function (IIEF) and a global efficacy question (GEQ: Did treatment improve your erections?).

Results. For the group, the mean baseline IIEF score before therapy was 29.7 ± 9.8. After intracavernosal therapy (mean dose 34.7 ± 7.3 μg), IIEF improved to 36.1 ± 11.4 (17.7%). After addition of doxazosin, IIEF improved to 48.6 ± 13.4, 46.4 ± 10.9, and 51.5 ± 14.3 at 4, 8, and 12 weeks, respectively ($P < 0.01$). The GEQ response improved from 25.7% at baseline to 81.4% at 12 weeks. Overall 22 (57.9%) of 38 patients with the combined regimen had a significant (more than 60% improvement in IIEF) therapeutic response.

Conclusions. The addition of an oral alpha-blocker may have a beneficial effect in patients with erectile dysfunction for whom intracavernosal therapy alone fails. The synergistic effects of vascular dilation and blockade of sympathetic inhibition may explain this response. The potential role of alpha-blockade in synergy with other agents designed to treat erectile dysfunction remains to be determined. UROLOGY **52:** 739–743, 1998.

According to recent epidemiologic studies, as many as 30 million men in the United States suffer from some degree of compromised erectile function.[1] This number will be significantly increased with the continued aging of the American population. Current treatments for erectile dysfunction include oral medications, intracavernosal injections, transurethral applicators, vacuum pumps, vascular surgery, and penile prostheses.[2–6]

Intracavernosal injections of vasoactive agents result in relaxation of both cavernous and arterial smooth muscle.[4] This results in filling of the penile sinusoids by blood while concomitantly restricting venous outflow. Agents used for intracavernosal injection therapy include papaverine, phentolamine, and alprostadil.[4,7–9]

Alprostadil (a synthetic prostaglandin E_1) is the most widely used agent and has been demonstrated to be effective in treating men with erectile dysfunction.[4] The use of alprostadil results in vasodilation, smooth muscle relaxation, and inhibition of platelet aggregation. Roy *et al.*[10] demonstrated that alprostadil is metabolized by the enzyme 15-hydroxydehydrogenase, which is active in the human

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corpus cavernosum. Linet *et al.*[4] reported in a dose-response study that all doses of alprostadil were superior to placebo, with a significant dose-response relation. In a 6-month self-injection study in 683 men, sexual activity was reported after 94% of the injections. Combination treatments (ie, phentolamine plus papaverine and/or alprostadil) are also often used. These combinations may increase efficacy and reduce the rate of side effects.[11,12] Nevertheless, there is a significant dropout rate with these therapies because of side effects and the lack of efficacy.[13]

Adrenergic receptors exist in the brain centers associated with penile erection, libido, and ejaculation. Agents that affect these receptors have been extensively studied and used in the therapeutic management of erectile dysfunction. Oral use of the $alpha_1$-adrenergic antagonist phentolamine is currently being investigated as a treatment option in men with erectile dysfunction. Becker *et al.*[14] recently reported that in select populations oral phentolamine might be of benefit. In addition, Grimm *et al.*[15] reported that in the TOMHS (Treatment of Mild Hypertension Study) analysis, the incidence rate of erectile dysfunction was lower in the alpha-blocker group (doxazosin) than in the placebo group. Yohimbine (an $alpha_2$-adrenergic antagonist) has been demonstrated to have moderate efficacy in men with psychogenic erectile dysfunction. Its role in organic erectile dysfunction is minimal.[3,16]

The purpose of this pilot study was to determine the potential role of oral alpha-blockers in combination with intracavernosal therapy in men with erectile dysfunction for whom intracavernosal therapy alone failed.

MATERIAL AND METHODS

Study Subjects

Thirty-eight men with chronic erectile dysfunction who were unable to achieve a spontaneous erection sufficient for intercourse at any time within the preceding 6 months were enrolled into this open, prospective study. Patients were self-referred and not randomized. Exclusion criteria included patients with significant cardiovascular disease, major psychiatric disorder, poorly controlled diabetes mellitus, or a history of intolerance to alpha-blockers.

Study Design

This open-label, flexible-dose, nonrandomized study was carried out in 38 men who met the entry criteria. The etiology of erectile dysfunction was assessed by history and physical examination. All patients had previously been treated with various doses of intracavernosal alprostadil (Caverject) with little or no response (on the basis of patient definition). Treatment doses of alprostadil were at the discretion of the treating physician. All the men had previously been trained to inject themselves. All 38 men described little or no response to therapy.

At entry to the study, all patients received daily doxazosin titrated to 4 mg over 3 weeks. During this 3-week period, patients were told to not use intracavernosal injection. At the end of the titration period, patients could then resume use of intracavernosal injection when planning to have sexual activity in addition to daily doxazosin.

TABLE I. *Baseline demographic characteristics*

Characteristic	Mean	Range
Age (yr)	61.7 ± 9.8	41–75
Partner age (yr)	54.3 ± 8.7	26–71
Duration of dysfunction (mo)	34.6 ± 6.8	7–49
Etiology of erectile dysfunction (% of men)		
Organic	79.3	
Psychogenic	8.7	
Mixed	12	
Concomitant conditions (% of men)		
Hypertension	27.4	
Ischemic heart disease	6.5	
Diabetes	17.5	

Study of Efficacy and Safety

Efficacy was assessed at baseline and at 4, 8, and 12 weeks after doxazosin titration using the 15-item, self-administered International Index of Erectile Function (IIEF).[17] Specific questions analyzed included the frequency of penetration (Q3) and the frequency of maintained erections (Q4), with responses graded on a scale of 1 (almost never or never) to 5 (almost always or always). Specific domains analyzed included erectile function, orgasmic function, sexual desire, and intercourse satisfaction. In addition, a global efficacy question (Did treatment improve your erections?) was assessed.

During each clinic visit, supine and sitting blood pressure measurements were done. Open-ended questions were asked to elicit information regarding adverse medical reactions.

Statistical Analysis

The mean and standard deviation at each time point were calculated for all parameters. Paired *t* tests were used to assess changes from baseline. The mean frequency of responses to questions 3 and 4 of the IIEF for each treatment group were calculated. An analysis of covariance model was fitted for each question. The answers of each treatment group to the global efficacy question were analyzed with the use of logistic regression analysis. Intent to treat analysis was performed on all variables.

RESULTS

The demographic characteristics of the men studied are listed in Table I. Before injection therapy, the mean baseline IIEF score was 29.7 ± 9.8. After intracavernosal therapy, IIEF improved to 36.1 ± 11.4 (17.7%). After addition of doxazosin, IIEF improved to 48.6 ± 13.4, 46.4 ± 10.9, and 51.5 ± 14.3 at 4, 8, and 12 weeks, respectively ($P < 0.01$). The mean scores for questions 3 and 4 of the IIEF were significantly higher for the group after combination treatment than for intracavernosal therapy alone ($P < 0.02$) (Table II). The per-

TABLE II. *Improvement in frequency of penetration (Q3) and frequency of maintained erections (Q4) using combination therapy**

Question	Baseline	4 Weeks†	8 Weeks†	12 Weeks†
Q3 (mean)	2.47 ± 1.1	3.87 ± 1.4	3.79 ± 0.9	3.99 ± 0.9
Q4 (mean)	2.14 ± 0.9	3.46 ± 1.3	3.78 ± 1.2	3.68 ± 1.2

** Question 3 (Q3) and question 4 (Q4) of the International Index of Erectile Function, graded on a scale of 1 to 5 (almost never or never to almost always or always).*
† $P < 0.02$.

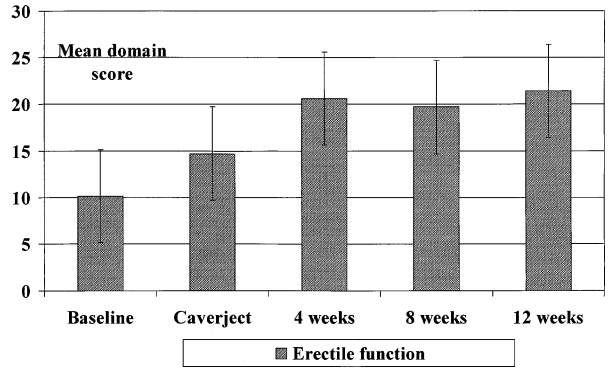

FIGURE 1. *Mean scores for the erectile function domain of the IIEF (six questions: possible total score of 1 to 30).*

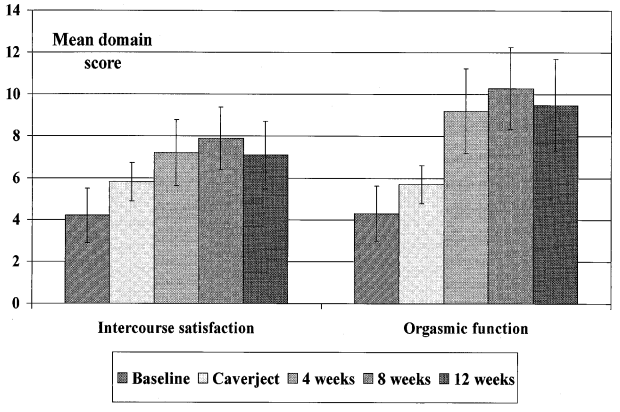

FIGURE 2. *Mean scores for the orgasmic function domain (two questions: possible score of 0 to 10) and the intercourse satisfaction domain (three questions: possible score of 0 to 15) of the IIEF.*

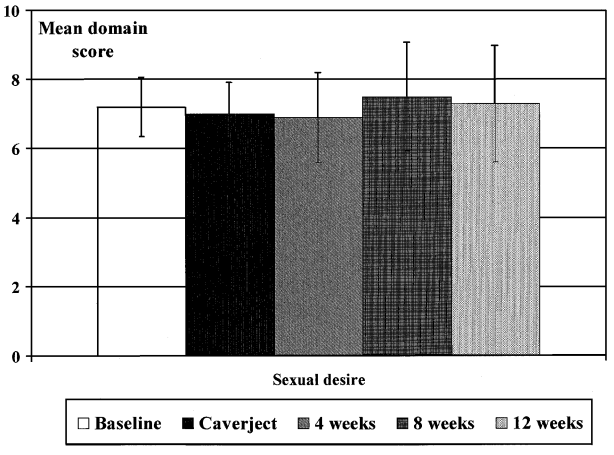

FIGURE 3. *Mean scores for the sexual desire domain (two questions: possible score of 2 to 10) of the IIEF. There was no effect of treatment on sexual desire.*

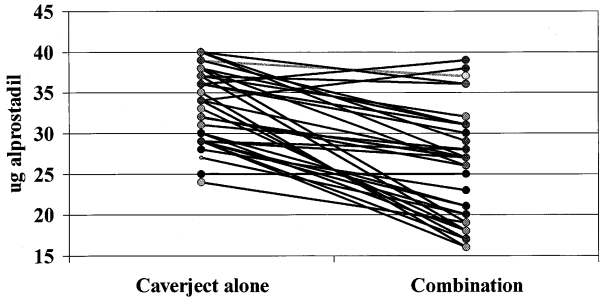

FIGURE 4. *Change in alprostadil dose in individual patients.*

cent increase was 61.5% for question 3 and 71.9% for question 4.

The mean scores for the erectile function domain of the IIEF increased with combination therapy ($P < 0.01$) (Fig. 1). Similarly, the mean scores for the orgasmic function and intercourse satisfaction were also significantly higher ($P < 0.004$) (Fig. 2). There was no effect on sexual desire with either intracavernosal therapy alone or in combination with oral alpha-blockade (Fig. 3).

Global efficacy increased from 25.7% at baseline to 71.2%, 79.4%, and 81.4% at 4, 8, and 12 weeks, respectively. Overall 22 (57.9%) of 38 patients with the combined regimen had a significant (more than 60% reduction in total IIEF) therapeutic response.

Before instituting combination therapy, the mean dose of alprostadil was 34.7 ± 7.3 μg. At 12 weeks, the mean dose decreased to 23.5 ± 4.3 μg. The distribution of dosing change is shown in Figure 4.

Of the 38 patients, 3 (7.9%) had significant side effects (dizziness 2; asthenia 1) requiring withdrawal from the study. All 3 had significant improvement in erectile function (IIEF increased 72.3%) before withdrawal.

COMMENT

The number of therapeutic agents either available or under investigation for the treatment of

erectile dysfunction has increased over the past decade. These include the widespread use of yohimbine, the agent sildenafil recently approved by the Food and Drug Administration, other oral agents in clinical trials, including phentolamine and apomorphine, and intracavernosal agents such as alprostadil, papaverine, and phentolamine.[1–14,16,18]

In an effort to both increase efficacy and diminish side effects, combination treatments such as papaverine plus phentolamine and alprostadil; and phentolamine plus papaverine or alprostadil have been advocated.[19] Padma-Nathan[20] conducted a blind study comparing prostaglandin E_1 and papaverine with phentolamine and prostaglandin E_1 and concluded that the triple mixture was superior.[20] By contrast, Meinhardt *et al.*[11] found that there was no obvious difference between a combination of either three or two agents. However, to date there have been no studies that have investigated the potential combination of both an oral and intracavernosal agent.

Oral alpha antagonists have been touted as a potential therapy for erectile dysfunction. Yohimbine, an $alpha_2$-adrenoreceptor antagonist, has long been used as a treatment for erectile dysfunction.[3,16] In a study of patients with psychogenic erectile dysfunction, a 62% response rate compared with a 16% response rate in the placebo group was observed.[21] It is generally accepted that the efficacy of yohimbine is minimal. Phentolamine is a nonspecific $alpha_1$-adrenoreceptor antagonist that inhibits the action of both epinephrine and norepinephrine. This results in a reduction of sympathetic tone and concomitant relaxation of both arterial and corporal smooth muscle. These physiologic phenomena result in an increased blood flow into the sinusoidal spaces of the penis and compression of trabecular smooth muscle against emissary veins.[14]

Gwinup[22] reported that 5 of 8 patients who took phentolamine before placebo reported success. By contrast, of the 8 patients taking placebo first, 2 responded. Similarly, Zorgniotti[23] reported a 42% rate of full spontaneous erections using 50 mg of phentolamine. More recently, Becker *et al.*[14] reported the results of a double-blind, placebo-controlled study in 40 men with recent onset of erectile dysfunction treated with varying doses of phentolamine. Full erections were achieved by 20% of the placebo group, 30% with 20 mg, 50% with 40 mg, and 40% with 60 mg. The potential efficacy of other oral alpha-blockers has not been investigated. However, recently Grimm *et al.*[15] reported the long-term effects on sexual function of five antihypertensive drugs in the TOHMS analysis. Doxazosin, an alpha-blocker used in both the treatment of hypertension and benign prostatic hyperplasia, was found to have a lower incidence of erectile dysfunction (2.8%) compared with placebo (4.9%) after 24 months. In addition, when analyzing men who entered the study with erectile dysfunction, the rate of cessation was highest in the placebo group.

The results of the present study, albeit in a small sample, suggest that the use of a combination of an oral alpha-blocker with an intracavernosal agent significantly increases efficacy. Moreover, the population studied was a group who had a minimal or poor response to an intracavernosal agent alone. This represents one of the first studies to analyze the role of combination therapy using various routes of therapy.

The rationale for the combination therapy proposed herein is twofold. The tone within the corpus cavernosal tissue is primarily controlled by two systems. The prime determinants are the sympathetic noradrenergic system, which controls detumescence, and the noradrenergic, noncholinergic system, which, by release of nitric oxide, activates the aforementioned erectile response. The sympathetic innervation of the cavernosal tissue is predominantly through the $alpha_1$-adrenoreceptor subtype.[24] In addition, there is a significant effect from direct injection of doxazosin into the cavernosal tissue of monkeys. The erectile response is dose-related and not due to systemic drug exposure, because circulating drug levels were not detected (Wyllie M, personal communication). Therefore, alpha-blockade by agents such as doxazosin may help potentiate the stimulatory effect of prostaglandins by removing inhibitory responses mediated by the sympathetic nervous system.

The data reported herein do not support the use of doxazosin alone in the management of erectile dysfunction. Nevertheless, a number of potential issues can be raised. (1) What is the potential role of oral alpha-blockers with other agents such as transurethral alprostadil? (2) Does combination therapy allow for lowering the dose of intracavernosal agents, thereby minimizing side effects? (3) What is the potential role of combining various oral agents (ie, an alpha-blocker with either sildenafil or apomorphine)? (4) Would the same results be achieved if doxazosin had been taken at a lower dose and on an intermittent basis?

Clearly, the cost of managing erectile dysfunction is increased when multiple agents are used. This is particularly true if agents must be used on a daily basis (eg, doxazosin). However, given the significant concomitant incidence of hypertension, benign prostatic hyperplasia, and erectile dysfunction, pharmacologic agents that may have more than one effect, such as alpha-blockers, may become more attractive options for treatment.

CONCLUSIONS

The results of this preliminary study suggest a synergistic role between oral alpha-blocking agents and vasoactive intracavernosal agents. This suggests that the "stimulatory" effect of vasoactive agents can be potentiated by removal of sympathetic inhibitory tone. Whether these results can be duplicated in larger and more varied populations remains to be determined.

As the treatment of erectile dysfunction becomes more medically oriented, it is also clear that monotherapy will fail in some patients. As in other clinical conditions such as hypertension, benign prostatic hyperplasia, and prostate and bladder cancer, where combination therapy is routinely advocated, the potential enhancement of erectile dysfunction therapy by using combination agents represents an exciting future area of research.

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