

Prospective Study Comparing Hyoscyamine, Doxazosin, and Combination Therapy for the Treatment of Urgency and Frequency in Women

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Anticholinergics are commonly used for the treatment of frequency, urgency, and urge incontinence in women. Alpha-blockers have been shown to have a modulating effect on bladder smooth muscle but are not commonly used clinically for this indication. To evaluate the clinical effectiveness of each treatment as well as the combination therapy, we performed an open prospective study comparing these agents. Between September 1994 and October 1995, 34 women aged 28–91 (mean age, 62) received either 0.375 mg of sustained-release hyoscyamine twice a day or 2 mg doxazosin QHS prior to being crossed over to the other drug and/or the combination. Symptoms were assessed using an expanded American Urological Association (AUA) symptoms score, which included questions regarding incontinence at completion of each therapeutic phase. Evaluation included 6-channel urodynamics. All three therapies were noted to be effective in reducing AUA symptom scores. By urodynamic evaluation, a greater percentage of patients with increased voiding pressures or decreased compliance responded to doxazosin than hyoscyamine. Side effects were noted to be less prevalent with doxazosin than with the other therapies. There appears to be a significant role for alpha-blockers in the treatment of voiding symptoms in women. *Neurourol. Urodyn.* 16:31–36, 1998. © 1998 Wiley-Liss, Inc.

Key words: urgency; frequency; drug therapy; urodynamics; AUA symptom score

INTRODUCTION

Women have been shown to develop urinary frequency, urgency, and urge incontinence with increasing age [Burgio et al., 1991; Jolleys, 1990; Stanton et al., 1983]. These symptoms have traditionally been treated with anticholinergic agents, with mixed success and significant side effects. Several large controlled studies demonstrated the usefulness of alpha-1 blockers for the treatment of voiding symptoms in men [Lepor et al., 1992; Di Silverio, 1992; Lloyd et al., 1992]. Recently, scores from the American Urological Association (AUA) symptom index have been shown to be equivalent in men and women between ages 50–79 [Lepor and Machi, 1993]. This observation suggests that the development of increased urinary symptoms may not be gender specific but may be due to common underlying etiologies that have yet to be completely elucidated. This led us to consider using alpha-1 blockers in the

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treatment of voiding symptoms in women. We performed a prospective study comparing traditional anticholinergics with newly recognized alpha-1 blockers for the treatment of urgency and frequency in women.

METHODS

From September 1994 until February 1996, 34 women, aged 28–91 (mean age, 62), received either 0.375 mg of sustained-release hyoscyamine twice a day or 2 mg doxazosin QHS prior to being crossed over to the other drug and/or the combination. Patients were placed on each therapy for a minimum of 1 month. A detailed history, physical examination, urinalysis, and 6-channel urodynamics were performed on each patient prior to treatment. Symptoms were assessed at baseline and at the completion of each therapeutic phase, using an expanded AUA symptom score that included questions regarding incontinence (Fig. 1). Side effects were assessed after each treatment phase and scored on a 0–3 scale. A voiding pressure >30 cm of water was considered elevated.

Statistical Analysis

Data were analyzed using descriptive statistics. Each therapeutic option was compared to baseline using two-sided paired Student's *t*-tests. Comparison testing was also used when applicable. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 34 patients was enrolled. Thirty-one patients received hyoscyamine, 25 patients received doxazosin, and 13 patients received combination therapy. Patients who achieved a good response to a particular treatment and did not want to be crossed over were included in the statistical analysis.

Mean baseline AUA symptom score was 19. Sixty-eight percent of the women improved on hyoscyamine alone, 68% improved on doxazosin alone, and 77% improved with combination therapy. Mean improvement in AUA symptom score over baseline was 34% ($P < .001$), 30% ($P = .002$), and 48% ($P = .004$) for hyoscyamine, doxazosin, and the combination, respectively.

In our study, 50% of women not responding to hyoscyamine responded to doxazosin or the combination. Conversely, 38% of women not responding to doxazosin responded to hyoscyamine or the combination. There was one patient who responded to the combination but not the individual drugs.

Adverse effects are reported in Figure 2. These side effects were reported as none, mild, moderate, or severe for each category. In the anticholinergic group, side effects included dry mouth, constipation, dizziness, tiredness, headaches, vaginal dryness, and night sweats. Side effects in the alpha-blocker group included dry mouth, diarrhea, constipation, dizziness, tiredness, headaches, and leg edema. In all, 19 women (61%) reported moderate-to-severe side effects with hyoscyamine, 8 (47%) with doxazosin, and 8 (61%) with combination therapy.

Urodynamics was performed on 32 of the 34 patients, with 2 patients refusing. A higher percentage of women with elevated voiding pressures on urodynamics responded to doxazosin than hyoscyamine. Patients with decreased compliance were also more likely to improve on doxazosin than on hyoscyamine (Fig. 3). Comparison tests did not show statistically significant differences for the above-mentioned urodynamic data ($P > 0.05$).

Over the past month, how often have you:

1. Had the feeling of not emptying your bladder completely after urinating?
Not at all <1 time in 5 <Half the time About half the time > Half the time Almost always
2. Had to urinate again less than 2 hours after you finished urinating?
Not at all <1 time in 5 <Half the time About half the time > Half the time Almost always
3. Found you had stopped and started again several times when you urinated?
Not at all <1 time in 5 <Half the time About half the time > Half the time Almost always
4. Found it difficult to postpone urination?
Not at all <1 time in 5 <Half the time About half the time > Half the time Almost always
5. Had a weak urinary stream?
Not at all <1 time in 5 <Half the time About half the time > Half the time Almost always
6. Had to push or strain to begin urination?
Not at all <1 time in 5 <Half the time About half the time > Half the time Almost always
7. On average, how many times do you urinate during the night?
2 4 6 8 10 >10
8. On average, how many times do you get up to urinate during the night?
2 4 6 8 10 >10
9. If you were to spend the rest of your life with your condition just the way it is now, how would you feel about that?
Delighted Pleased Mostly Satisfied Mixed Mostly Dissatisfied Unhappy Terrible

If your urinary problem is incontinence (ACCIDENTS):

10. How often do you have accidents?
<Once a month A few times a month A few times a week Almost everyday Everyday
11. How heavy are the accidents?
A few drops Damp underwear Moderate wetting Sometimes soaking Always soaking
12. Do you know when it is going to happen?
Always Most of the time Half the time Sometimes Never
13. Can you prevent the accidents?
Always Most of the time Half the time Sometimes Never
14. How long have your accidents caused you problems?
Up to 1 month Up to 1 year Up to 2 years Up to 5 years Up to 5 years More than 5 years
15. How often do you change your pads per day?
Do not use 1 2 3 4 5
16. If you use incontinence products, how much do you spend per week on these product (pads, etc.)?
\$ _____ Do not know No cost, covered by insurance Do not use these products

Fig. 1. Modified AUA symptom score.

DISCUSSION

Anticholinergics are commonly used for the treatment of frequency, urgency, and urge incontinence in women. These drugs have been traditionally used because irritative voiding symptoms in women were thought to be due to overstimulation or overresponsiveness of the bladder by the parasympathetic nervous system. Statisti-

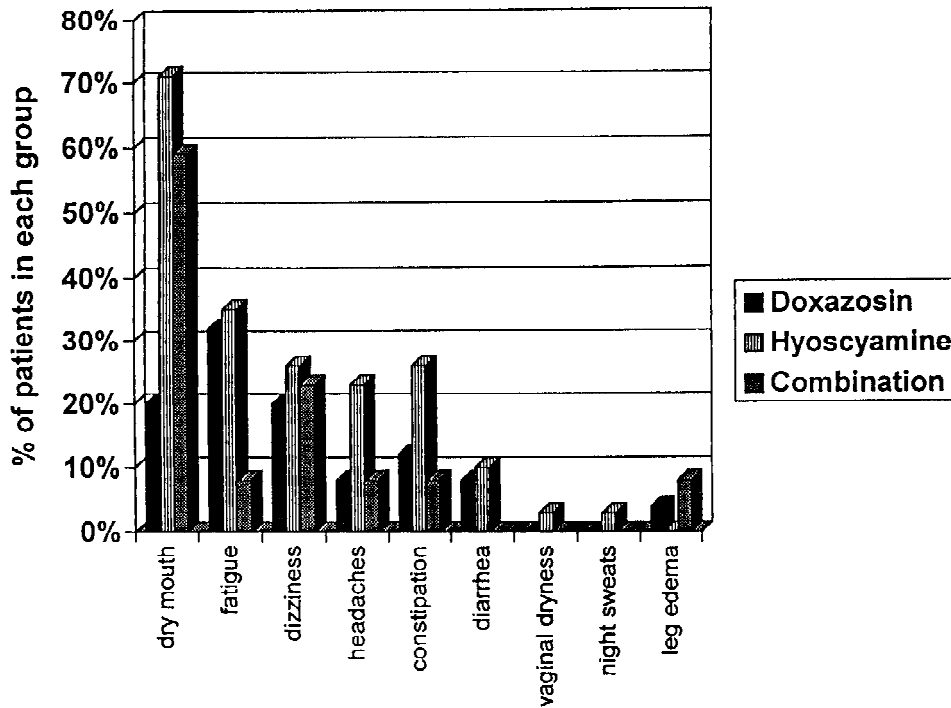


Fig. 2. Percentage of patients in each treatment group who experienced significant side effects.

cally, these agents have been shown to be more effective than placebo, but this response is variable. Oxybutynin, for example, was shown to improve symptoms in 60% of women as compared to 2.3% with placebo [Moore et al., 1990]. This finding was reported earlier by Moisey et al. [1980], who showed a 69% response with oxybutynin and a 9% response with placebo. Similarly, when terodiline was used to treat detrusor instability, 62% of patients improved compared to a 42% improvement with placebo [Tapp et al., 1989]. This lack of therapeutic response in all patients suggests that other nonparasympathetic-mediated mechanisms may be responsible for these symptoms. Two possible mechanisms have been previously proposed to explain noncholinergic-mediated irritative voiding symptoms [Wein, 1989, 1992]. The first is dysfunction of the bladder neck or urethra, which leads to secondary decreased detrusor compliance, analogous to symptoms of benign prostatic hypertrophy (BPH). A second possibility is overstimulation of alpha receptors or upregulation of these receptors in the body of the bladder.

Swierzewski et al. [1994] demonstrated that incontinence and hyperreflexia decreased in spinal cord injury patients with the use of terazosin while bladder compliance improved. They concluded that the improvement in symptoms with alpha-blockers was due to a direct influence on the detrusor muscle. In contrast, Lepor and Theune [1995] recently examined this issue and found that terazosin is no better for the treatment of irritative voiding symptoms than placebo. This study evaluated 29 women with prostatism-like symptoms. Urodynamics was not performed, so voiding pressure or compliance data were not available. Lepor and Theune [1995] concluded that alpha-blockers affect mainly the bladder outlet, and since there was no response

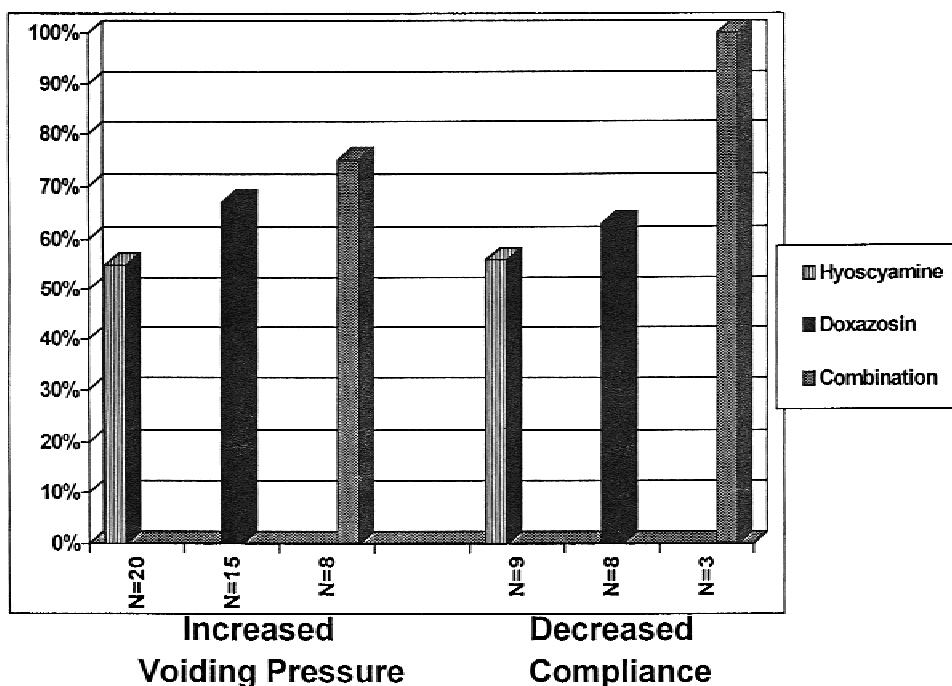


Fig. 3. Percentage of women with increased voiding pressure or decreased compliance who responded to each therapy.

compared to placebo, they inferred that voiding symptoms of women are mostly due to a detrusor problem.

We compared doxazosin to hyoscyamine and combination therapy. Our study demonstrated that there were three classes of responders: alpha-blocker responders only, anticholinergic responders only, and responders to both individual treatments. A significant percentage of all women who did not respond to one agent responded to the other, which further supports the idea of multiple mechanisms being responsible for irritative symptoms. Alpha-blocker responders were more likely to have elevated voiding pressures or decreased compliance. These underlying mechanisms are not mutually exclusive and can be found in the same individual. This fact is evidenced by a mean symptom improvement of only 33% and 30% for hyoscyamine and doxazosin, respectively, which increased to 48% with the combination therapy.

Side effects were noted to be prevalent with both therapies. More women complained of side effects with anticholinergics and were more likely to rank these side effects as moderate-to-severe. Combination therapy did not lead to more side effects than anticholinergics alone. It would thus be advantageous to try alpha-blockers first, if possible, to avoid this higher rate of adverse effects.

Our study used a modified AUA symptom score to measure baseline symptoms and response to treatments. While this symptom score has been validated in men [Barry et al., 1992] and used extensively in recent literature, it has been largely ignored in studies concerning women. Thus, this lack of a standardized reporting tool has made retrospective comparison of treatments in women difficult. Our use of the

AUA symptom score in this study allows for a more intuitive and useful presentation of the data. We therefore encourage greater use of the AUA symptom score in future studies involving women. Furthermore, our urodynamic data, though statistically not significant, may be clinically useful in predicting who will respond to different medications. Perhaps with a larger sample size, these findings may in fact prove to be statistically relevant.

In conclusion, we found that alpha-1 blockers are useful in the treatment of voiding symptoms in women. Given the side-effect profile, alpha-blockers may be the best starting therapy for all women. With the use of urodynamics, one may be able to predict the subset of women most likely to respond to a given therapy. Consequently, studies in the future should be directed at pursuing the etiology of female frequency, urgency, and urge incontinence, and at using various combinations of drugs to treat female voiding symptoms.

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