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Effect of Terazosin on Urine Storage and Voiding in the Aging Male With Prostatism

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Patients in a private practice, evaluated for prostatism due to benign prostatic hypertrophy were offered the options of medical treatment with the alpha blocker terazosin, surgical treatment, or continued observation. Nineteen men accepted terazosin treatment and are the subjects of the present series. They were treated over a mean period of 8 months, the longest treatment lasting over 22 months. Dosage was started at 1 mg/d and increased as tolerated to 2, 5, and 10 mg/d over the test period. Extensive testing including invasive urodynamics, multiple voiding diaries, and symptoms scores at each dosage level was carried out. We found that flow rates increased moderately from baseline in a dose dependent fashion. At the 10 mg/d dosage some patients achieved flow rates in the low normal range. Patients on treatment documented a decrease in the number of voidings per day, a decrease in nocturia, an increase in bladder capacity and the volume of each voiding. On the other hand, patients frequently did not appreciate changes in their voiding patterns, as reflected in their responses to the symptom questionnaires. We could not demonstrate significant changes in bladder pressures on cystometry either during filling or voiding. Our data suggested that terazosin may well have a direct effect on the fundus of the aging bladder to increase capacity, and, through the well-known relationship between voided volume and flow rate, increase urinary flow rate. © 1994 Wiley-Liss, Inc.

Key words: prostatism, terazosin, urine storage and voiding

INTRODUCTION

The finding of alpha adrenergic receptors in the smooth muscle of the prostate and bladder base [Caine et al., 1975; Levin and Wein, 1979; Raz et al., 1973] has kindled considerable interest in the medical treatment of obstructive prostatism due to benign prostatic hyperplasia. The investigations of phentolamine and phenoxybenzamine by Caine et al. [1976, 1978, 1981] have been followed by studies of other alpha adrenergic blockers such as prazosin [Hedlund and Anderson, 1988; Kirby et al., 1987] and terazosin [Dunzendorfer, 1988; Lepor, 1990; Lepor et al., 1990; Fabricius et al., 1990]. These agents have demonstrated an effect of increased flow

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rates and improved symptom scores presumably through their effect on the bladder neck and prostate. However, the relief of symptoms is not completely explained by the improvement in flow rate alone, since despite statistically significant percentile increases in flow, the flow rates seldom move into the normal range at the dosages which were tested. We suggest that the alpha blocker terazosin may have a clinically beneficial effect on the fundus of the bladder, which is not generally appreciated. The present study employs extensive testing of a small number of patients in hopes of uncovering more details of the physiological effect of terazosin in the obstructed aging patient.

MATERIALS AND METHODS

Nineteen men with symptoms of prostatism due to benign prostatic hypertrophy accepted a treatment program employing terazosin as the primary treatment. The diagnosis of obstructive benign prostatic hypertrophy (BPH) was made clinically in a large group of patients by physical examination, cystoscopy, and, in some subjects, by supplementary intravenous urography. Cystometrograms and pressure-flow studies were not done prior to initiation into the program. Patients in whom there was no contraindication to terazosin were offered three treatment options: surgery, continued observation, or medical treatment with terazosin. The patients who chose terazosin are the subjects of the present study. The members of the terazosin cohort were subjected to repetitive investigative procedures prior to the administration of terazosin and at different dosage levels. All men volunteered willingly for the study as approved by our hospital based IRB. They were offered no incentives other than the medication which was provided at no charge. Terazosin was administered at increasing dosage levels starting at 1 mg/d for several days and then going to 2 mg/d. This dosage was maintained in most for a period of about 2 months before increasing to larger dosages. As the study matured and we developed more experience with terazosin, we shortened the time at 2 mg/d to 2 to 3 weeks. The 5 mg dosage was maintained for several months initially, but again we shortened the time to advancement to 10 mg/d to several weeks, as we became more comfortable with the medication. Once the subjects settled on the final dosage, we tested for baseline differences among the groups. None were detected. Voiding diaries and symptom scores were obtained at every change of dosage and at intervals of about 2–4 months during a period of unchanging dosage. Cystometrograms and pressure-flow studies were obtained initially and after 6–9 months, though later in the study the follow-up CMGs were done at 3 months since patients progressed to their final dosage much earlier. Additional studies were done on several patients at more than one dosage level, extending over 12–14 months.

Uroflowmetry

Fifty-six flow rates were performed on 19 patients. Patients were asked to drink a liter of water during the hour prior to the test and were then asked to void into the urinary dynamometer. Flow rate, volume voided, and stream force were recorded. Residual volume was measured by catheterization immediately following the dynamometer study and prior to administration of the cystometrogram.

Cystometry

Fifty-one cystometrograms were performed on 17 patients. A 14 French (Fr) foley catheter with a 5 Fr ureteral catheter inserted in its tip was inserted into the bladder in the supine position. The bladder was drained and the resting pressure measured. A rectal balloon for the measurement of intraabdominal pressures was placed and cutaneous electrodes were placed over the anal sphincter for EMG recording. The patient was then asked to sit on the micturition chair. The bladder was filled with water at a rate of 50–60 ml/min; bladder pressure, volume infused, rectal pressures, and EMG activity were monitored. When the bladder was filled, the foley catheter was removed and the patient was asked to void around the 5 Fr ureteral catheter. Urinary flow rate, volume voided, bladder pressure, rectal pressure, subtracted detrusor pressure, and EMG activity were recorded simultaneously. After completion of the test, residual volume was determined by ultrasound measurement.

Voiding Diary

Patients were requested to record the time of voiding and the amount voided for each micturition over a 3 day period. Subjects voided into a standard measuring cup graduated in ounces and recorded time and volume on a form we provided. Eighty-eight studies were done on 19 patients.

Symptom Score

Patients were asked to fill out symptom scores at intervals of several weeks and especially after changing medication dosage. The scores included the usual symptom questions based on the Boyarsky questionnaire [Boyarsky et al., 1976] and were graded to a total score of 28 (Appendix A). Eighty-seven symptom scores were collected from 19 patients.

Terazosin was administered in increasing dosage starting at 1 mg and progressing to 2 mg thereafter for 6 weeks or longer. The dose was then increased to 5 mg given each morning for 4 to 6 weeks, whereupon some patients were moved to 10 mg given in 5 mg doses twice a day. If a patient did not tolerate an increase of dosage he was kept at whatever dosage he found comfortable. The final dosage was 2 mg in 7 patients. These stopped at this low level because they were satisfied with their response, developed symptoms at higher dosages, or in one case left the study in favor of surgery after several months. Nine patients were brought to a final dosage level of 10 mg/d. Three patients stopped at 5 mg/d, final dosage.

The longest duration of treatment was 22 months with a mean duration of 8 months. The age of the men ranged from 53 to 82 years with a mean age of 66 and a median of 68 years.

Statistics

We elected to study a small number of patients intensively, rather than study a large number superficially. The present number was selected prospectively since it was large enough to be reliably analyzed by non-parametric statistics specifically

selected for treatment of small series, and yet, was small enough to permit study of multiple variables repetitively without becoming unwieldy or excessively costly.

All data were entered into a standard spread sheet program and, in part, in a locally produced statistical analysis program. Each item of the symptom score was entered separately as was each datum of the voiding diary. Data were abstracted from the urinary flow rate and from the filling portions and voiding segments of the cystometrogram. Each patient was treated as a single data set unit of analysis, multiple tests with the same control parameters were averaged, and the resulting data were subjected to statistical analysis.

The primary statistical tool was the non-parametric Smirnov-Komolgorov two-sample test [Sachs, 1984], probably the most efficient procedure for determining the differences between treatments with small samples. Where useful, means and standard deviations were calculated. When the Smirnov test gave inconclusive results (because the probability of the occurrence of the test parameter fell between $P = 0.05$ and $P = 0.10$), the data were retested with the Fisher-Behrens test for equality of the means with unequal variances [Sachs, 1984] and, if possible, with a form of the Chi-square two sample test [Sachs, 1984]. If at least two tests yielded similar marginal conclusions, the combined result was reported as adumbrating but not confirming significance and possibly indicating a real trend that should be retested in the future with a larger sample; if $P \geq 0.20$ we felt confident that it was very unlikely that the result was significant or that the study of larger numbers would achieve significance in spite of the low power of the technique.

In testing the individual elements of the symptom score, the Chi-square test was the primary tool as the test best suited for studying contingency tables with discrete categories. Although the continuous distributions were tested for normality, no importance was attached to the results because the Smirnov test is non-parametric and the two other procedures are very robust against deviations from the normal. All statistical procedures were chosen for their validity for small samples. Given the small size of the sample and the exploratory nature of the statistical tests and, consequently, of our inability to fix the numerical alternative assumptions a priori, the powers of the tests were not calculated and, as it turned out, were not needed. A posteriori power calculations were not made because we did not plan to confirm our marginal findings with larger samples.

RESULTS

Voiding Diaries (Table I, Fig. 1, and Appendix B)

Tabulation of about 260 days of recorded voidings measuring the time of voidings and the amounts, revealed a reduction in the average number of voidings per 24 hours among the treated patients. This seemed to be dose dependent and was most clearly seen at the 10 mg/d dosage wherein the number of voidings was reduced by nearly 30%. Mean volume voided at each micturition also increased (Fig. 1). Patients who started out with small voided volumes (i.e., < 120 ml) increased to mid-sized voidings (120–180 ml). Patients starting at mid-range volumes increased to large volumes (> 180 ml). The net result was a shrinkage of the small volume voided subset with a concomitant increase in the large volume voided subset. The mid-range subset did not change as the number entering was approximately equal to the number leaving. Again the effect was most marked in the 10 mg cohort.

TABLE I. Voiding History Summary (n = 19)*

Category	Mean ± SD		P
	Pretreatment	Treated	
Total no. of voidings	10.8 ± 2.5	8.8 ± 1.9	0.0048
Volume per void	153 ± 39	204 ± 63	0.0029
Less than 120 ml	5.3 ± 3.2	.6 ± 1.8	0.0021
121 ml to 180 ml	2.9 ± 1.0	2.4 ± 1.2	0.0647
More than 180 ml	2.6 ± 1.9	4.9 ± 2.7	0.0166
10 pm to 6 am	2.9 ± 1.1	2.2 ± 1.2	0.0342
Volume/day	1,664 ± 504	2,107 ± 762	0.0567

*Using $P = 0.05$ as the rejection level it is seen that nocturia improves significantly. Low volume voidings have diminished and high volume voidings have increased significantly which indicates a major shift to higher volumes. Mid-range voiding and volume/day may be considered to differ marginally and could possibly be shown to differ significantly with a larger sample. Although the actual comparisons and statistical decisions in Tables I, III, and IV were made by means of the Smirnov-Komolgorov procedure, we present only the means and standard deviations for the sake of brevity.

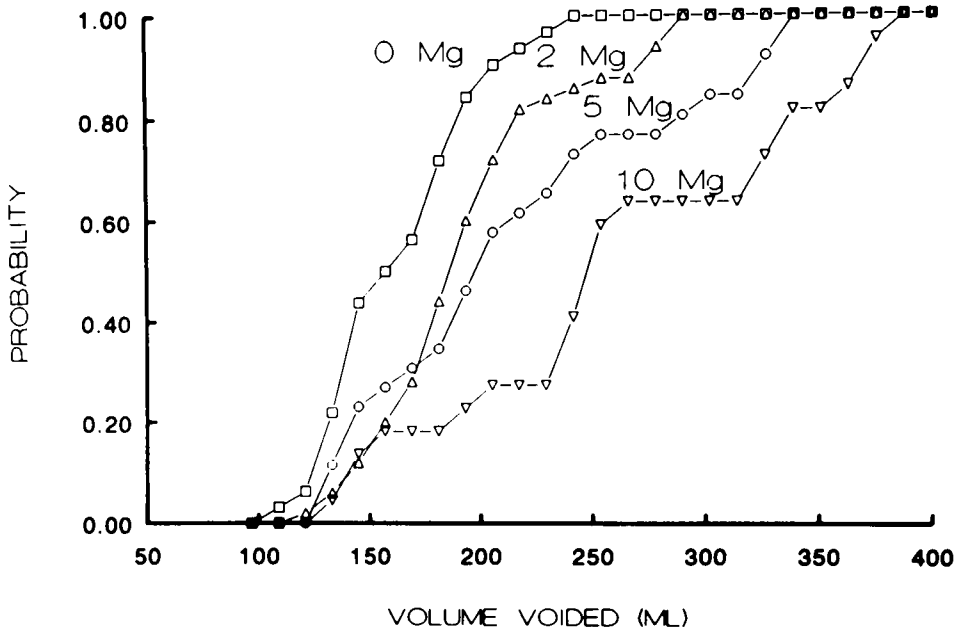

Fig. 1. Probability that an average volume voided per micturition (volume for 24 hours divided by number of voidings in 24 hours) is equal to or less than a specific volume as a function of dosage. Cumulative distributions for all doses appear to be different from the 0 mg distribution and to move toward the larger volumes. The 5 and 10 mg curves differ statistically from the 0 mg distribution at $P = 0.041$ and $P = 0.0002$, respectively. The 2 mg curve differs at $P = 0.10$ but not at $P = 0.05$. The difference is probably real but needs to be tested with a larger sample. The line symbols in the figure are introduced to identify the lines especially where there is overlap. They were generated by the computer during integration, and do not correspond to data points.

TABLE II. Symptom Scores: Comparison of Treated and Untreated Groups (n = 19)†

Item	Chi^2	d.f.	*P*
Total score	4.24	3	0.37*
Stream strength	4.27	2	0.12**
Straining	0.95	1	0.33
Hesitation	3.15	2	0.21
Intermittency	3.60	2	0.17
Bladder emptying	0.58	3	0.90***
Incontinence	4.15	2	0.13
Urgency	0.50	3	0.92
Nocturia	3.11	3	0.53****
Frequency	3.23	3	0.44

†Symptom scores were collected in the same patients at all dosage levels tested.

*–****There was no statistically significant perception of difference in this series between the treated and untreated subjects even though at the 10 mg level symptoms were significantly improved (*P = 0.00; **P = 0.11; ***P = 0.04; ****P = 0.02). Since symptom scores are not drawn from continuous distributions, comparisons were made with contingency tables and the associated chi-square test. d.f. = degrees of freedom.

Symptom Scores

When comparing the pretreatment test scores with those at the end of treatment 8 to 24 months later, we found no statistically significant improvement at the 2 and 5 mg/d dosage schedule. At the 10 mg/d dose level patients were aware of improvement of stream size and completeness of emptying. Nevertheless, for the majority of patients symptom score results were disappointing in that patients did not appreciate improvement which was clearly demonstrated in the voiding diaries (see Appendix B). Results are summarized in Table II and Figure 2.

Cystometrogram (CMG) Data

Patients forced liquids prior to testing and presented in a state of urgency. We obtained two flow rates: the first prior to the CMG, and the second after filling the bladder as part of the CMG. The latter voiding occurred with a 5 French (Fr) ureteral catheter in place. We did not find a statistically significant difference between the two flow rates. Although peak flow rate for the entire group increased significantly, the changes were most evident in the 10 mg cohort. There was also a significant reduction in the post void residual volume. Surprisingly, detrusor pressures during filling and during voiding were not affected by terazosin. The pressure at first desire during filling, the premicturition pressure, and the voiding pressure were so very nearly unchanging with treatment that it is unlikely that larger numbers of cases would alter this finding. Resting pressure was noticeably reduced. Opening pressures tended lower with terazosin, but, noting that the variance of opening pressure was large and that a large number of studies would be necessary to confirm these findings, we prefer to offer no conclusion. Phasic contractions during filling, if present prior to treatment, were absent or diminished in number, or occurred later in filling and at larger volumes in most patients treated with terazosin. Cystometrogram data are summarized in Tables III and IV.

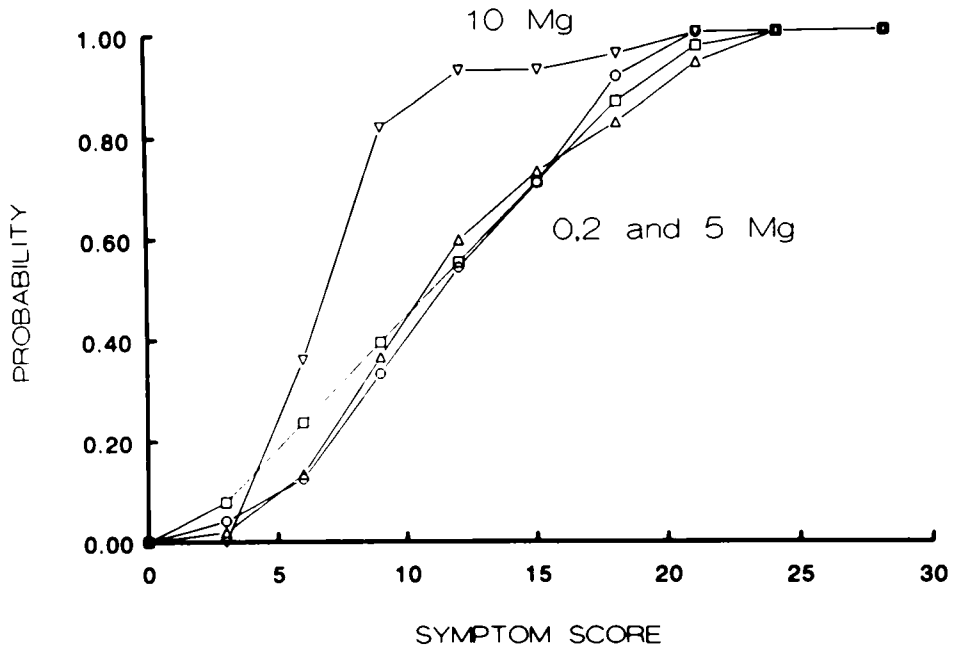

Fig. 2. Probability that a symptom score is equal to or less than a specific value as a function of dosage. The total perception of change reported by the patient was negligible at 2 mg and 5 mg. Note how the three cumulative distributions for 0 mg, 2 mg, and 5 mg superimpose. At 10 mg patients report improvement. Note how the 10 mg cumulative probability distribution is displaced toward the lower scores. The difference between 0 mg and 10 mg is significant ($P = 0.00011$).

TABLE III. Post-CMG Uroflowmetry Data*

	Mean ± SD		
Category	Pretreatment (n = 17)	Treated (n = 16)	*P*
Volume voided (ml)	353.8 ± 162.0	391.8 ± 119.6	0.2240
Residual volume (ml)	205.3 ± 118.6	102.2 ± 72.1	0.0026
Bladder capacity (ml)	246.0 ± 130.3	308.4 ± 136.3	0.0946
Maximum flow (ml/s)	7.8 ± 3.7	12.8 ± 3.7	0.0007

*Patient voids around 5 Fr ureteral catheter. Post-void residual volume diminishes and the maximum flow rate increases significantly with terazosin.

TABLE IV. Mean Pressures Delivered by Detrusor as a Function of Terazosin Administration*

		Mean ± SD			
Pressure at	n	Pretreatment	n	Treated	*P*
Rest	18	34.22 ± 5.46	17	30.76 ± 5.25	0.03
First desire	18	40.89 ± 14.02	17	37.00 ± 6.94	0.15
Premicturition	18	52.55 ± 26.03	17	46.94 ± 14.67	0.22
Maximum flow	18	80.37 ± 20.16	17	80.37 ± 21.18	0.46
Opening	17	45.58 ± 14.99	14	53.57 ± 16.88	0.09
Closing	17	30.76 ± 31.30	14	44.29 ± 16.98	0.12

*The difference of 3.46 cm H_2O in the resting pressure is significant at the $P = 0.05$ level; it is tempting to postulate that this may play a role in the increasing bladder capacity induced by terazosin in the voiding diaries. For all practical purposes we must conclude that aside from the resting pressure, terazosin does not affect bladder pressures. A retesting of the data with the Smirnov-Komolgorov two sample test confirms the conclusions.

DISCUSSION

Although the present study was not placebo controlled, the series of symptomatic patients was intensively and repetitively studied over a prolonged period of time. The absence of meaningful change in many parameters is fairly conclusive and would not likely be modified by either placebo control or a larger sample. Although no conclusions could be made about changes in a very few parameters, terazosin did induce a number of clearly significant changes both subjectively and objectively.

Only 7 patients accepted the 10 mg doses and 6 showed significant increases in flow rate and diminution of symptoms. The remaining patients were divided between those who found satisfactory relief of symptoms at lower doses, or would not tolerate increasing doses at the 5 or 10 mg level.

Was the salutary effect of the terazosin on voiding related to a decrease of outlet resistance alone or were other mechanisms also involved? There is evidence that alpha blockade induces relaxation of the intrinsic sphincteric musculature of the prostatic urethra. A stromal element comprises the significant portion of prostatic substance and this is rich in smooth musculature densely populated with alpha-1 adrenergic receptors [Lepor and Shapiro, 1984]. Blockade of these neurohumoral receptors induces relaxation of prostatic smooth muscle in the laboratory and clinical setting. Similarly, in another study, pressure in the human prostatic urethra was measured by urethral profile [Furuya et al., 1982] and relaxation was demonstrated with alpha blockade. The diminution of post operative urinary retention [Tammela, 1986] following alpha blockade demonstrates a beneficial effect of administration of such agents clinically. However, decreased outlet resistance during voiding may not be the sole mechanism of improved voiding. The presence of increasing alpha adrenergic receptor activity in the body of the aging bladder is demonstrated in the rat [Lin et al., 1992]. Though this finding has yet to be demonstrated in the human it is a very attractive working hypothesis. Since alpha adrenergic activity in the bladder is associated with increasing muscular tone and therefore wall tension, blockade of these receptors would be expected to relax the detrusor fibers and result in larger bladder capacity, decreased resting pressure, and increased volumes per voiding (all found on the present study). During cystometric filling, terazosin also reduced the number of phasic contractions or shifted them to the right. It seems very reasonable to us that terazosin had a direct salutary effect on the detrusor enhancing urine storage. Furthermore, since increased bladder filling results in increased detrusor stretch, which in turn improves detrusor contractility [Schafer, 1990], the flow rate would be expected to improve on this basis alone. This after all, is the theoretical basis of the well-known flow rate–volume voided relationship [von Garrelts, 1956]. We tested the validity of this hypothesis in our series by normalizing the peak flow rate against the volume voided and patient age with an appropriate nomogram [Drach et al., 1982]. The maximum flow rate was adjusted to a "standard flow rate" that eliminated the effects of volume and age. Comparison of the pre- and post-treatment volume corrected flow rates (Fig. 3) demonstrated that the difference between their dose related cumulative distributions was very negligible ($P > 0.7$). With so great an upper tail area the power of the test is so enhanced that it is highly unlikely that a larger study will disprove this finding. One can then directly relate the improvement in voiding symptoms, such as decrease in urgency, frequency, nocturia, etc., to this therapeutic increase in bladder capacity which we postulate relates to a blockade of alpha recep-

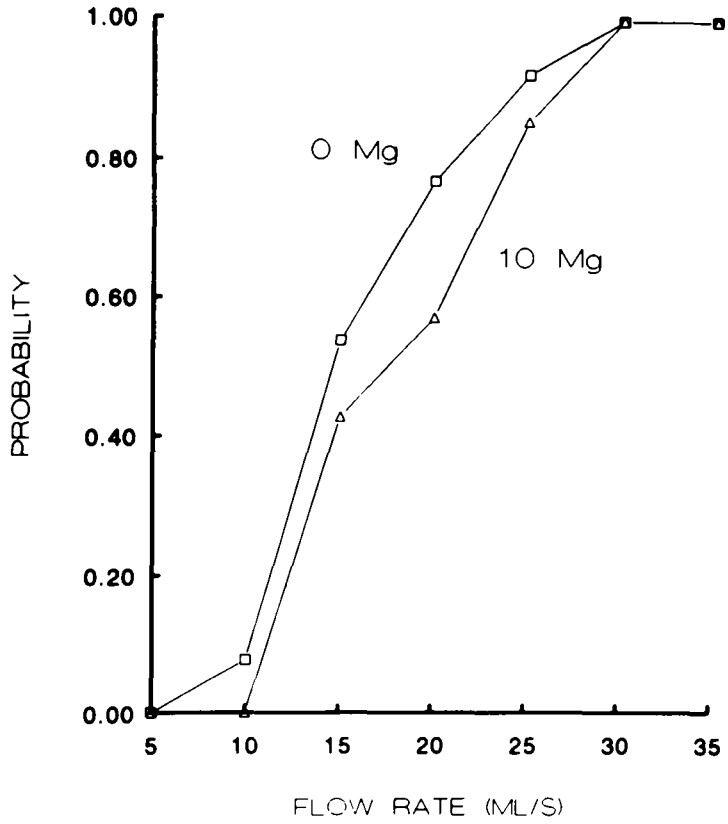

Fig. 3. Cumulative distributions of peak flow rates adjusted for age and volume for the 0 mg and 10 mg cohorts. The small separation between the two curves is not significant at $P > 0.70$ (nearly certain). This result suggests that the variation of flow rate with dosage is, to a great extent, explainable as a consequence of increased volume voided and bladder capacity.

tors in the body of the aging obstructed bladder. On the other hand, there was no clear trend toward reduction of bladder voiding pressures, which would have been expected with improvements in flow of the magnitude demonstrated [Meyhoff et al., 1989]. The reduction of opening pressures may be real but will require larger numbers to verify significance. We also studied whether bladder compliance, a visco-elastic effect, was modified by terazosin but could not demonstrate a significant change between the treated and pretreated cohorts ($P > 0.7$). Thus, we offer an alternative suggestion that in addition to its effect on the bladder outlet, terazosin has a direct effect on the detrusor through blockading alpha adrenergic neuroreceptors which we hypothesize occur in the body of the aging bladder, thereby enhancing bladder capacity and, consequently, detrusor contractility and voiding efficiency.

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APPENDIX A. Symptom Score Form

Stream	How would you describe your urinary stream?	0 Normal 1 Variable 2 Weak 4 Dribbling
Voiding	Have you had to strain or push over your bladder to urinate?	0 No strain 3 Abdominal strain
Hesitancy	Have you noticed you can't begin urination well?	0 No 3 Hesitancy
Intermittency	Does your stream stop and start 2 or more times while you urinate?	0 No 2 Yes
Bladder emptying	How would you describe your ability to empty all of the urine out your bladder? (have you ever had your bladder catheterized?)	0 Don't know 0 Complete 1 Variable 2 Incomplete 3 Single retention 4 Repeated retention
Incontinence	Have you noticed dribbling or urinating after you thought you were finished?	0 No 2 Yes (include terminal dribbling)
Urge	Have you had the feeling you can't wait to urinate?	0 No 1 Mild 2 Moderate 3 Severe 4 Uncontrolled voiding
Nocturia	How often do you have to interrupt your sleep to urinate?	0 0–1 1 2 2 3–4 3 More than 4
Diuria	How often do you have to urinate during the day?	0 Once every 3 hr 1 Once every 2 hr 2 Once every hr 3 More than once an hr

APPENDIX B. COMPARISON OF SYMPTOM SCORES WITH VOIDING DIARIES

Although it is not the purpose of the present study to validate or invalidate patient generated symptom scores, it may be of some interest to test two diagnostic features that are easily compared by means of the voiding diaries filled by patients in conjunction with symptom scores: nocturia and frequency. The perceived score was obtained directly from the patients' written report and we then calculated a corresponding score from the voiding diaries collected during the same time interval (Table 5). The Kappa statistic was used to test how well the symptom scores could be used to predict the observed scores. We used the Landis criterion for evaluating Kappa [Rosner, 1986]:

$$K > 0.75 \text{ denotes excellent reproducibility}$$
$$0.4 \leq K \leq 0.75 \text{ denotes poor reproducibility}$$
$$0.0 \leq K \leq 0.40 \text{ denotes very poor reproducibility}$$

TABLE V. Comparison of Voiding Diary Reports With Empirical Measurements of the Same Parameters*

	Voiding diary scores			
Perceived score	0	1	2	3
Nocturia				
0	4	6	4	0
1	5	8	6	0
2	1	3	4	3
3	1	0	0	1
Frequency				
0	5	1	0	0
1	19	10	3	0
2	4	1	2	0
3	1	0	0	0

*Number of times a perceived score is matched by a voiding diary score recorded in the same time interval. The diagonal cells report the perfect matches whereas the off-diagonal cells contain the misses. In the frequency table we could eliminate the 3 scores without affecting the Kappa statistic very much.

For nocturia, empirical and perceived scores matched only 30.2% of the time and for frequency just 29.0% of the time. The Kappa statistics were 0.097 and 0.124, respectively, indicating very low reproducibility. We can state with some confidence that nearly 70% of the time the patients were not aware of significant changes in nocturia and frequency even though they had actually measured and recorded the volume and time of each voiding during the same time interval in which they filled out the symptom scores.