Efficacy and Safety of Doxazosin (CARDURA™) in the Management of Benign Prostatic Hyperplasia

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Abstract

Objective

To assess the efficacy and safety of the selective á$_1$-blocker doxazosin in black men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia.

Patients and Methods

An open-label study involving consecutive patients with benign prostatic hyperplasia. They were asked to complete the International Prostate Symptom Score (IPSS), with its eighth question (bother score) and perform basic uroflowmetry. The study involved the use of doxazosin for the treatment of symptomatic benign prostatic hyperplasia in three phases. Phase 1 of washout period/enrolment, a two weekly interval titration phase and a maintenance phase for four weeks. The symptom score (IPSS), bother score and uroflowmetry were used to evaluate the severity of the condition and the efficacy of the drug.

Results

Twenty-four patients were enrolled into the study, only 18(75%) completed the eight-week study. The ages of the patients ranged between 46 years and 82 years with a mean of 66 years. (SD, 10.0)

Fourteen patients were stabilized on 4mg doxazosin while the remaining 4 patients had 2mg. There was significant improvement of the symptoms, with a remarkable sharp decline after two weeks of medication in IPSS by 8 points from baseline. The improvement was sustained over the following six weeks period. The bother score (quality of life index) was similarly observed to decline from a mean of 4.7 at baseline to 1.3 at the end of the study. The clinical trial showed a significant increase in the urine flow rate with an improvement of 4mls/second from baseline and a 24.1% increase in voided volume.
There was no adverse event recorded in all the patients to warrant discontinuation of the study.

Conclusion

Doxazosin is an effective and well tolerated drug in the treatment of symptomatic BPH in Nigerians.

Key Words: BPH, LUTS, Quality of life, IPSS, a1-blocker, Doxazosin.

Introduction

Benign prostatic hyperplasia (BPH) is a common disease that affects men from middle age. Androgens and aging are necessary for the development of the disease and its progression [1].

BPH is not life-threatening but its clinical manifestation as lower urinary tract symptoms (LUTS) can be very bothersome and impact substantially on patients' quality of life (QOL). [2,3]
The severity of the symptoms can be quantitatively assessed by means of the International Prostate Symptom Score (IPSS), the bother score and the urine flow rate.

Various researches into BPH over the years have resulted in not only a clearer understanding of its pathogenesis, but also the development of medical and minimally invasive surgical treatments [4,5].

A significant component of symptons of BPH is believed to be related to smooth muscle tension in the prostate stroma, urethra, and bladder neck, mediated by á$_1$-adrenergic receptors.
Currently, α_1 blockers are the most effective first-line monotherapy for patients with BPH-related LUTS [6,7]. They produce a rapid and sustained symptom relief irrespective of prostate size.

Data from studies[7-9] have shown that all currently available $\alpha_1$blockers (Doxazosin, Terazosin, Alfuzosin, Tamsulosin) at therapeutic dose share similar efficacy, but differ in their tolerability and safety profiles.

Doxazosin, a quinazoline derivative and a selective inhibitor of the alpha 1 subtype of the alpha adrenergic receptors was studied in respect to its efficacy and safety in the management of benign prostatic hyperplasia in a black population.

The initial study reported from Nigeria[10] on the evaluation of this alpha 1 blocker in the management of BPH had used the International Prostate Symptoms Score (IPSS) as an outcome measure without any standard urodynamics assessment of the subjects. This study therefore evaluated the role of Doxazosin in the management of BPH in blacks using the urine flow rate and the responses to the IPSS indices as efficacy endpoints.

Patients and Methods

The study is an-open label prospective evaluation of the efficacy and safety of doxazosin in the management of benign prostatic hyperplasia. Written informed consent was obtained from each patient before entering into the study.

Included in the study were males 40 years and above with history of both storage and voiding symptoms, digital rectal examination finding in keeping with BPH and at least two of the following: IPSS $\geq$ 9, PSA $\leq$ 4ng/ml, Peak flow rate of <15ml/second, Voiding time of > 30 second.

Exclusion criteria included previous or suspected history of intolerance or hypersensitivity to Doxazosin or quinazoline derivatives or any alpha blocker, previous bladder/prostate surgery, suspected prostate cancer or bladder neck lesion, diverticula or urethral stricture, neurogenic bladder, urinary tract infection, urinary retention (acute & chronic), haematuria, patients with significant hepatic, renal and haematologic impairment. Patients with clinically significant heart failure, myocardial infarction, stroke, blood pressure greater than 160/100 mmHg or less than 90/60 mmHg, orthostatic hypotension or fluid depletion were also excluded as well as those on medications that may affect bladder function (anticholinergics).

All consecutive patients with benign prostatic hyperplasia who fulfilled the inclusion criteria were enrolled into the study. The study consists of three parts: the wash-out period, a titration phase and the maintenance period in an altogether 5 visits over 8 weeks.

The first part is a 2-week wash-out phase for initial screening assessment. Patients who had other form of treatment for BPH were tapered off over the first week in order to have a wash-out period of a minimum of seven days. Written informed consent was obtained, biodata, medical history as well as full physical examination findings documented. The serum PSA level was measured at this enrolment.

This was followed by titration phase of 2 weeks, when IPSS and bother score were assessed and baseline uroflowmetry performed. Branded Doxazosin (Cadura) 1mg was dispensed to the patients.

At subsequent maintenance phase of 2 weeks interval (Visits 3 & 4), doses of drug were escalated to 2mg and 4mg respectively depending on the response and tolerability, as determined by reviewed IPSS bother score and any adverse events. At final visit 5 after four weeks of optimum tolerated dose, the IPSS, bother score, adverse events and repeat uroflowmetry was performed and documented.

All patients who concluded the study were analysed. The various variables were analyzed separately for change from baseline using a paired t-test. Efficacy accepted when tests are statistically significant at the 5% confidence level.

Results

Twenty-four patients were enrolled at the urologic clinic of Lagoon Hospital Apapa, Lagos into the study. Eighteen (75%) completed the eight-week study. Fifteen of the patients were newly diagnosed patients while three were already on other treatments requiring washout.

The age range was 46-82 years and the mean age 66years (SD, 10.0). Eight (44.4%) patients were 70 yrs and above.

Fourteen patients were stabilized on 4mg doxazosin while the remaining four patients had 2mg. The frequency distribution of the international prostate symptom score (IPSS) at each visit during the study is shown in Table 1. There was a remarkable sharp decline in the total score at the 3rd visit but became gradual at each subsequent visit (Figure I); this was statistically significant.($P<0.01$) Symptom relief was rapid within the first 2 weeks of treatment as mean improvement was 44.4%.Both voiding and storage symptoms were significantly improved. All the patients had an IPSS $\leq$2(0-2) in intermittency, 17(94.4%) in incomplete emptying, 16(88.9%) in both weak stream and straining, whilst 15(83.3%) in frequency and 11(61.1%) in nocturia, within the first 2 weeks of doxazosin medication.

The quality of life index was observed to decline at every subsequent visit, with a significant improvement in bother score from a mean of 4.7 at baseline to 1.3 at the end of the study (Figure 2). This suggests that the drug might have affected the quality of life positively.

In all the patients that completed the study, with urodynamics, the voiding time decreased but not statistically significant (P>0.05).

However there was significant increase in voided volume and peak flow rate at the last visit.

Voided urine volume increased from a median of 174mls to 216mls, an improvement of 24.1%. Peak flow rate (Qmax) improved by 4ml/s. (Table 2). These significant changes could be attributed to the drug.

There was no adverse event that warranted discontinuation of the drugs. Only 2 (11.1%) patients complained of postural hypotension. probably due to vasodilation.

Table 1: Frequency Distribution of the International prostate Symptom Score (IPSS).

IPSS	**Visit**							
	2		3		4		5	
	n	%	n	%	n	%	n	%
1. Incomplete Emptying								
0 - 2	10	55.6	17	94.4	18	100	18	100
3 - 5	8	44.4	1	5.6	0	0	0	0
2. Frequency								
0 - 2	7	38.9	15	83.3	17	94.4	17	94.4
3 - 5	11	61.1	3	17.7	1	5.6	1	5.6
3. Intermittency								
0 - 2	13	72.2	18	100	18	100	18	100
3 - 5	5	26.8	0	0	0	0	0	0
4. Urgency								
0 - 2	7	38.9	14	77.8	17	94.4	17	94.4
3 - 5	11	61.1	4	22.2	1	5.6	1	5.6
5. Weak Stream								
0 - 2	9	50	16	88.9	17	94.4	18	100
3 - 5	9	50	2	11.1	1	5.6	0	0
6. Straining								
0 - 2	12	66.7	16	88.9	18	100	18	100
3 - 5	6	33.3	2	11.1	0	0	0	0
7. Nocturia								
0 - 2	2	11.1	11	61.1	15	83.3	17	94.4
3 - 5	16	88.9	7	38.9	3	16.7	1	5.6
Total	**18**		**18**		**18**		**18**	

Table 2: Summary Statistics of Uroflowmetry at each Visit.

Uroflowmetry	Visit	Summary Statistics						
		No of Subject	Mean	Std. Dev.	Median	Range	Mode	F	P-value
1. Voiding Time	2	18	53.67	27.20	49.50	(10, 105)	38.00	0.7875599	0.557621
	5	18	46.82	24.0	45.00	(19, 100)	19.00		
2. Voided Volume	2	18	192.11	66.28	174.00	(109, 345)	148.00	1.776342	0.081415
	5	18	243.29	101.51	216.00	(125, 444)	125.00		
3. Peak Flow rate	2	18	8.83	3.05	8.150	(3.5, 13.6)	7.200	3.226362	0.003125
	5	18	13.85	5.81	12.10	(7.9, 26.7)	8.600		

Figure 1: Line Graph showing the Total International Prostate Symptom Score (IPSS) at each visit.

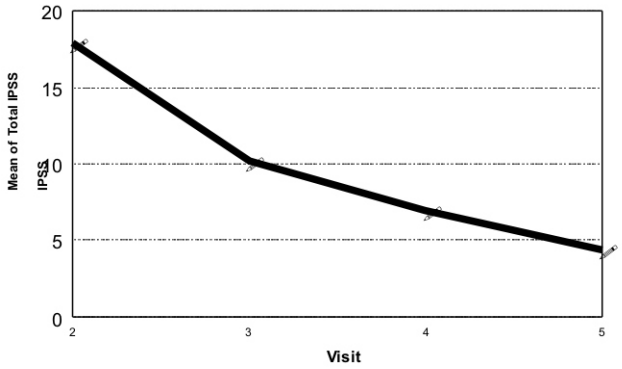
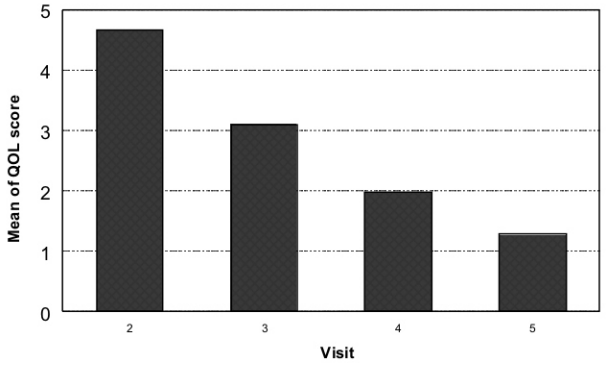


Figure 2: Bar Chart showing the Quality of Life Score (QOL) at each visit.



Discussion

Benign Prostatic Hyperplasia (BPH) is the most common benign neoplasm of the aging man. It is a pathologic process that contributes to lower urinary tract symptoms (LUTS) with a significant negative effect on quality of life.

Studies [11, 12] have shown a significant correlation between diminished urinary flow rate and BPH related LUTS.

The main pharmacological treatments for BPH are a1-adrenoceptor antagonists. These drugs are the most efficient first line monotherapy as they rapidly and effectively improve symptoms and quality of life [4, 13, 14].

Doxazosin (a second-generation, long-acting, a1-selective antagonist) allows once daily dosing. Clinical trials have demonstrated that it increases urinary flow rate by 23% to 28% and decreases symptom scores by 16.4% versus 9.8% in placebo groups in men with symptomatic BPH [15, 16]. These findings have been collaborated by this study. With compliance and appropriate dosage a linear relationship was observed between the symptoms and time of visit, as the visit increased the IPSS decreased. This resulted in the total IPSS improvement by a mean of 13.5 points from baseline.

Also nocturia, a particularly bothersome symptom was improved with Doxazosin, as evidenced by the decrease from 88.9% at baseline to 5.6% at the last visit, in percentage of patients waking up three or more times at night to urinate. The sustained efficacy on symptoms, nocturia and quality of life in this study is consistent with previously reported study of Nwofor and Dogunro[10]. At the last visit, the patients were happy with their quality of life.

The present study also confirms the efficacy of the drug on urine flow. There was a significant increase in the urine flow rate with a median improvement of 4mls/second from the baseline. The increased flow rate subsequently resulted in increased voided volume and a reduction in post-voiding volume.

The overall advantage of doxazosin in the study was the rapid onset of symptomatic improvement and efficacy in the patients independent of their prostate volume. The absence of significant adverse reaction in this study confirms the suitability of doxazosin in the management of BPH in blacks.

Nonetheless further studies involving large population will be necessary to corroborate the findings in this study.

Acknowledgement

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