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# DOXAZOSIN IN THE TREATMENT OF ELDERLY NIGERIAN MEN WITH BENIGN PROSTATIC HYPERPLASIA

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**Objective** To evaluate the efficacy and tolerability of doxazosin tablets in elderly patients with symptomatic benign prostatic hyperplasia (BPH).

**Patients and Methods** This study involved the use of doxazosin, a once daily alpha-1 adrenergic blocker, for the treatment of BPH in two distinct phases. Phase 1 involved a two-week dose titration, escalating from 1 mg to 8 mg depending on response and tolerability using blood pressure (BP) and pulse as a monitor to arrive at a stabilizing dose. In phase 2, the patients were maintained on the stabilized dose for 6 weeks. The International Prostate Symptom Score (IPSS) and Quality of Life Assessment (QLA) were used to evaluate the severity of the illness and the response to treatment. Twenty-six patients were enlisted while only 20 met the criteria for analysis. Mean age was 72.5 (55-90) years. Eighteen (90%) were stabilized at a doxazosin dose of 4 mg, while 2 (10%) stabilized on 2 mg.

**Results** There was a significant improvement of symptoms (IPSS) in all the patients at the end of the titration period, and this was progressive and sustained over the 6-week study period. QLA was also significantly improved. BP did not vary significantly in the normotensives, while the hypertensives required other antihypertensives to maintain normal levels. One case had severe postural hypotension that warranted discontinuation of the test drug. Using the Physician Global Assessment, efficacy was excellent in 65%, good in 30% and poor in 5%, while tolerability was excellent in 95% and poor in 5%. Drug compliance was 100%. Side effects were minimal and not life threatening.

**Conclusion** Doxazosin is effective in the treatment of BPH in elderly Nigerians. It is compatible with other drugs used in the treatment of other illnesses associated with old age. It is therefore recommended for use in elderly BPH patients.

**Keywords** Benign prostatic hyperplasia, doxazosin, alpha-1 adrenergic blocker, elderly patients

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is a disease associated with aging. Autopsy studies have shown that the histologic prevalence of BPH increases from 50% in men in their 6th decade of life to 90% in those above the age of 85 years[1]. A good proportion of this group develops prostatism as well as other chronic illnesses associated with aging like diabetes mellitus, hypertension and chronic chest infection. Because these are poor surgical risk patients, alternative modes of treatment for BPH have to be resorted to. Among these non-surgical options is medical treatment with alpha-1-adrenergic blockers which act on the alpha-adrenergic receptors in the prostate and bladder neck to produce relaxation of the smooth muscles, thus overcoming the dynamic component of benign prostatic obstruction[2,3].

This group of drugs has proven to be efficient in the management of BPH[3-8]. The earlier generation of alpha blockers, exemplified by prazosin which has a short half-life, rapid absorption and an early high trough level was shown to have side effects related to their pharmacokinetics, especially postural hypotension[6]. Moreover, the need for multiple daily dosing made compliance difficult. The development of long acting alpha-blockers, like doxazosin and terazosin, has reduced the side effect rate. This is especially true for doxazosin which has a half-life of 22 hours and a

**Table 1:** Associated Diseases in our BPH Patients

| Disease | No. | % |
|---|---|---|
| Hypertension | 6 | 30% |
| Diabetes mellitus | 2 | 10% |
| Arthritis | 3 | 15% |
| Chronic bronchitis | 1 | 5% |
| None | 8 | 40% |
| Total | 20 | 100% |

convenient once-a-day dosing[8,9]. It has a very good pharmacological profile; its absorption is slow and the serum level is sustained over a long period.[10].

Data from previous studies have established the efficacy and tolerability of doxazosin in the treatment of both BPH and hypertension[11,12]. The fact that it does not affect the blood pressure (BP) of normotensives also makes it suitable for the treatment of both hypertensive and normotensive patients with symptomatic BPH.

None of these studies, however, has been carried out in Nigerians. When recalling the inefficiency of prazosin in Nigerian hypertensives, it becomes imperative to establish the effect of doxazosin in Nigerians on both BPH and hypertension[13]. This study, therefore, aims to establish the efficacy, dosing and tolerability of doxazosin in Nigerians with BPH.

## PATIENTS AND METHODS

This open study of the effect of doxazosin on elderly men with symptomatic BPH was carried out over an eight-week period and included males aged 50 years and above with benign prostatic obstruction.

Patients with a previous history of hypersensitivity or intolerance to quinazoline derivatives, previous prostatic surgery or cases with other causes of bladder outlet obstruction like urethral strictures, carcinoma of the prostate, neurogenic bladder, urinary tract infection and urinary retention, as well as cases with significant hepatic, haematologic, renal and cardiac impairment were excluded from the study. Likewise, patients who had suffered from myocardial infarction or a cerebrovascular accident within the last 6 months, patients with a blood pressure of greater than 160/100 or less than 90/60, patients with uncontrolled or poorly controlled diabetes and patients on medications that may affect the bladder function like anticholinergics, cholinergics, beta-adrenergic blockers and diuretics were excluded. However, patients with chronic medical conditions that were clearly not associated with BPH or patients whose drug treatment was not likely to interact with the trial medication were included in the study.

A total of 26 patients was enlisted while only 20 met the criteria for analysis. Of these, 16 were newly diagnosed cases of BPH while 4 were washed out from prazosin treatment.

The mean age was 72.5 (55-90) years. The stabilizing dose of doxazosin was 4 mg for 18 patients (90%), while the remaining two patients (10%) were stabilized on 2 mg.

The associated illnesses are shown in Table 1.

The patients' history was documented. Special attention was given to the urinary symptoms using the International Prostate Symptom Score (IPSS) and Quality of Life Assessment (QLA) form[14]. This was followed by a thorough physical examination including digital rectal examination (DRE). Body weight, sitting and standing blood pressure (BP) and heart rate (HR) were documented at each visit.

Laboratory investigations were carried out at the beginning and at the end of the study. These included haematologic investigations (haemoglobin, haematocrit, platelet count, total and differential white cell count and erythrocyte sedimentation rate), chemistry (serum creatinine, blood urea, electrolytes, glucose, albumin, total protein, total bilirubin, alkaline phosphatase and other liver enzymes, and urinalysis) and microbiology (urine microscopy and culture).

The study period was 8 weeks divided into two phases after a one-week wash-out period for patients on other alpha-adrenergic blockers or other drugs affecting bladder function. The first phase was a 2-week titration period involving a doxazosin dose escalation from 1

**Table 2:** IPSS Score Over the Study Period

| | IPSS Score | | | | |
|---|---|---|---|---|---|
| S/N | Initial | Week 0 | Week 2 | Week 4 | Week 6 |
| 1 | 15 | 2 | 1 | 1 | 1 |
| 2 | 35 | 20 | 18 | 15 | 10 |
| 3 | 23 | 11 | 8 | 8 | 8 |
| 4* | 6 | 4 | 2 | 1 | 1 |
| 5 | 27 | 8 | 8 | 8 | 6 |
| 6 | 19 | 6 | 3 | 0 | 2 |
| 7 | 22 | 10 | 6 | 3 | 2 |
| 8 | 23 | 12 | 8 | 5 | 4 |
| 9 | 30 | 7 | 2 | 2 | 0 |
| 10* | 15 | 10 | 10 | 10 | 8 |
| 11* | 13 | 5 | 5 | 4 | 2 |
| 12 | 26 | 7 | 7 | 7 | 5 |
| 13 | 31 | 18 | 8 | 6 | 1 |
| 14 | 20 | 16 | 10 | 8 | 8 |
| 15 | 30 | | | | |
| 16 | 34 | 8 | 6 | 6 | 4 |
| 17 | 35 | 11 | 8 | 5 | 3 |
| 18 | 18 | 10 | 5 | 5 | 7 |
| 19 | 6 | 3 | 2 | 2 | 1 |
| 20 | 26 | 10 | 8 | 8 | 6 |

* washed out cases

**Table 3:** Quality of Life Assessment

| | Quality of Life Assessment | | | | |
|---|---|---|---|---|---|
| S/N | Initial Week -2 | Week 0 | Week 2 | Week 4 | Week 6 |
| 1 | 3 | 1 | 0 | 0 | 0 |
| 2 | 5 | 3 | 2 | 2 | 2 |
| 3 | 5 | 3 | 2 | 2 | 2 |
| 4 | 2 | 2 | 1 | 1 | 0 |
| 5 | 4 | 2 | 2 | 2 | 2 |
| 6 | 4 | 2 | 2 | 1 | 1 |
| 7 | 4 | 2 | 2 | 1 | 1 |
| 8 | 4 | 3 | 2 | 2 | 1 |
| 9 | 5 | 2 | 1 | 1 | 0 |
| 10 | 3 | 3 | 3 | 3 | 2 |
| 11 | 4 | 2 | 2 | 1 | 1 |
| 12 | 4 | 2 | 2 | 2 | 2 |
| 13 | 5 | 3 | 2 | 1 | 1 |
| 14 | 5 | 3 | 2 | 2 | 2 |
| 15 | 5 | | | | |
| 16 | 5 | 2 | 2 | 2 | 1 |
| 17 | 5 | 3 | 2 | 1 | 1 |
| 18 | 3 | 2 | 1 | 1 | 2 |
| 19 | 3 | 1 | 1 | 1 | 1 |
| 20 | 3 | 2 | 2 | 2 | 2 |

mg to 8 mg single daily dosing depending on the response and toleration of the doses as determined by the monitoring parameters. This was followed by a 6-week maintenance phase where the optimum tolerated dose as per phase 1 was maintained.

Assessment was done at two-weekly intervals using the following parameters: sitting and standing BP and HR, body weight as well as symptom quantification using IPSS and QLA, and laboratory investigations.

The efficacy and tolerability were evaluated on the last day of therapy using the Physician's Global Assessment scale.

Adverse drug reactions and other complications were documented where applicable.

## RESULTS

The symptom scores (IPSS) obtained over the study period are shown in Table 2. At the end of the titration period, all the patients had a significant improvement. This improvement was progressive and sustained at 6 weeks.

The quality-of-life values (Table 3) also show a significant subjective improvement in all the patients that completed the study.

There was no significant change in the blood pressure in the normotensive patients, while the hypertensive patients still required other drugs to maintain normal levels. The mean change in diastolic pressure was 3.4 mm Hg while in the systolic pressure it was 3.3 mm Hg.

One patient had severe postural hypotension warranting discontinuation of the drug. This resolved when the drug was discontinued.

Using the physician's global assessment, the efficacy was excellent in 65% (13 patients), good in 30% (6 patients) and poor in 5% (1 patient), while toleration was excellent in 95% (19 patients) and poor in 5% (1patient).

Drug compliance was 100%, while a minor adverse reaction of postural hypotension was seen in only one patient (5%).

## DISCUSSION

BPH is a common cause of urinary obstruction in the aging male. Its treatment ranges from open surgery to medical treatment over the years. Though transurethral prostatectomy has been regarded as the gold standard for the treatment of BPH, newer methods of treatment are being developed. Some of these are less invasive and are targeted at those who are not fit for surgery due to other illnesses or those who do not want surgery.

Among these are the medical options making use of the fact that BPH obstruction has two components: the static component which is due to the gland compressing the urethra, and the dynamic component which is due to alpha-1 adrenergic mediated smooth muscular contraction of the bladder neck and the prostate gland[3]. Thus alpha-1-adrenergic blockers are used to counteract this effect.

The alpha-1-adrenergic blockers have been well established as a medical option for the treatment of BPH[1-10]. The earlier adrenergic blockers were not very selective and as such had a number of other systemic effects like postural hypotension and erectile dysfunction. The newer generation exemplified by doxazosin, which is a more selective alpha-1-adrenergic blocker, has fewer side effects and is, therefore, better tolerated[9-12]. The once-daily dosing regimen of doxazosin has shown superiority over the multi-dose regimen by improving patients' compliance[10]. All these facts have been supported by this study in a Nigerian population with a 100% compliance being an evidence of good toleration of the drug.

The efficacy of the drug is also confirmed by the sustained improvement in both symptom scores and the subjective quality of life in the patients. This is similar to the results obtained in other studies.[15-17] The patients were able to get back to their usual activities which had been disrupted by the symptoms prior to treatment.

At the effective dose, no significant blood pressure change was noted. This is similar to the observation made by Kaplan et al.[17] who noted that, unlike other agents, doxazosin causes minimal change on the BP of normotensives and controlled hypertensives. These dosages have been noted to be lower than those required for effective treatment of hypertension in our environment.[18] Most hypertensives in the study required other antihypertensive drugs at a standard dosage range to control their blood pressure during the study period. This suggests that BPH may in fact increase the doxazosin dose required to control the BP in hypertensives. The absence of adverse reactions following these drug combinations is similar to the observation of others who demonstrated that doxazosin is compatible with other anti-hypertensives[10]. Similarly, in elderly patients with other chronic diseases like diabetes mellitus and chronic chest conditions, the drug treatment as well as the dosage was not affected by doxazosin.

A minor adverse reaction in the form of postural hypotension was noted in only one patient during the running-in period. The drug treatment was discontinued despite some improvement of his symptoms because of the nature of his job.

In conclusion, doxazosin seems to be an ideal treatment for such frail elderly BPH patients with debilitating illnesses that exclude surgery as a treatment option.

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## RESUME

### La Doxazosine dans le Traitement de l'Hypertrophie Bénigne de la Prostate chez les Patients Agés

**Objectif** Evaluer l'efficacité et la tolérance de la doxazosine chez des patients âgés présentant des symptômes d'hypertrophie bénigne de la prostate. **Patients et Méthodes** Cette étude porte sur l'utilisation de la doxazosine, un alpha-1 bloquant en prise unique journalière pour le traitement de l'HBP en deux phases. La première phase consistait en deux semaines de recherche de la dose appropriée avec une prise progressive de 1mg à 8 mg selon la réponse et la tolérance en mesurant la pression artérielle et le pouls jusqu'à arriver à une dose de stabilité. Dans la seconde phase, les patients sont maintenus à cette dose de stabilité pendant 6 semaines. Les scores internationaux des symptômes prostatiques (IPSS) et Qualité de vie (Qol) ont été utilisés pour évaluer la sévérité de la maladie et la réponse au traitement. Sur les 26 patients enrôlés, seuls 20 présentaient des critères analysables. L'âge moyen était de 72,5 ans avec des extrêmes de 55 et 90 ans. La stabilisation des symptômes a été obtenue chez 18 patients (90 %) avec la doxazosine 4mg tandis que 2 patients (10 %) l'ont été à la dose de 2 mg. **Résultats** Il y' avait une amélioration significative des symptômes (IPSS) chez tous les patients à la fin de la première phase, et de façon progressive et durable à la fin des 6 semaines de l'étude. La qualité de vie était significativement améliorée. La pression artérielle n'avait pas subi de variation significative chez les patients normotendus alors que le rajout d'autres anti-hypertenseurs était nécessaire pour obtenir une tension normale chez les patients hypertendus.

Un patient a eu une hypotension orthostatique sévère qui a amené à discontinuer le test thérapeutique. Le résultat était excellent dans 65 % des cas, bon dans 30 % des cas et faible dans 5% des cas. La tolérance était excellente dans 95 % des cas et mauvaise dans 5% des cas. La compliance au traitement était de 100%. Les effets secondaires étaient minimes et ne mettaient pas en péril le pronostic vital. **Conclusion** La Doxazosine est efficace chez les Nigérians âgés. Elle est compatible à d'autres médications utilisées dans le traitement des tares associées au vieillissement. Aussi, est-elle recommandée dans le traitement de l'hypertrophie bénigne de la prostate chez la personne âgée.

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