Indian J Physiol Pharmacol 2004; 48 (4) : 419–427

BARORECEPTOR MEDIATED BLOOD PRESSURE REGULATION IS NOT AFFECTED DURING DOSE DEPENDENT INHIBITION OF PROSTATIC CONTRACTIONS BY TERAZOSIN

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(Received on April 15, 2004)

Abstract : Benign prostatic hyperplasia (BPH), common in aging males is often treated with α_1–adrenoceptor (AR) antagonists. In view of known hypotensive effect of most of the α_1–AR antagonists, this work examined the effect of a selected α_1–AR antagonist, terazosin on the baroreceptor mediated regulation of blood pressure. The three doses of terazosin (10, 100, 300 µg/kg body weight) used in anesthetized dogs inhibited in a dose-dependent manner the prostatic contractions and rise in blood pressure induced by phenylphrine. Impairment of arterial baroreflex, an important neural regulatory mechanism for the maintenance of normal arterial pressure, by α_1–AR antagonist (prazosin) has been suggested in an earlier study. Hence, the effects of terazosin in doses 10, 100 and 300 µg/kg on baroreflex sensitivity (calculated as the ratio of heart rate change to acute increase in blood pressure by phenylephrine) were investigated. Terazocin did not produce any change in the baroreflex sensitivity. Therefore, in the absence of any adverse effect on the baroreceptor mediated regulation of the blood pressure, terazosin can be treated as a safer drug for the symptomatic treatment of BPH.

Key words : benign prostate hypertrophy, baroreflex, α_1–adrenergic receptors, terazosin

INTRODUCTION

The benign prostate hypertrophy (BPH), mainly affecting the older males is a hormone-dependent condition, initially manifested by the appearance of periurethral nodules followed by progressive enlargement of the prostate leading to a disturbance in normal urinary outflow, urinary retention and associated irritative symptoms (1–3). In symptomatic BPH two components are associated with urethral obstruction : a static component related to prostatic tissue mass and a dynamic component related to the sympathetic tone of prostatic and urethral smooth muscle (2, 4). This later component is due in part to the presence of the prostatic capsule (unique to humans), which tends to increase urethral resistance as a consequence of

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tissue expansion (5). The role of prostatectomy in the treatment of BPH has been scrutinized more critically owing to the prevalence of this condition, the cost of prostatectomy, the complications associated with this procedure (incontinence, stricture formation, impotence, epididymitis etc.) and the increasing interest generally in non surgical treatment alternatives.

The α_1–adrenoceptors (AR) are located in smooth muscle cell membrane of peripheral blood vessels, bladder neck, prostate capsule and prostate fibromuscular stroma. Stimulation of α_1–adrenoceptors activates the release of calcium within smooth muscle cells, resulting in smooth muscle contraction. The contractile response of prostatic smooth muscle through α_1–adrenoceptors located on stromal tissue has been well demonstrated (2, 6–10). Since the dynamic component of the prostatic smooth muscle tone is maintained exclusively via α_1–adrenoceptors, it seems likely that this tone will be largely mantained via the α_1–adrenoceptors. In this context evidence indicates that an increase in α_1–adrenoceptors density can be detected in BPH tissue (11, 12) associated with muscular stroma rather than glandular epithelium (13). However, in a study on quantitative analysis of mRNA no upregulation of α_1–adrenoceptors or downregulation of β–adrenoceptors was found in the bladder of patient with benign prostatic obstruction (14). Furthermore, smooth muscle strips taken from human hyperplastic prostatic tissue have been found to be more responsive to the α_1–agonist phenylephrine (PE) than the normal tissue (10, 15), which is consistent with clinical observations demonstrating that the extent of urinary flow improvement with α_1–adrenoceptor antagonists is directly related to the density of prostatic smooth muscle mass (16, 17). It has been suggested that adrenoceptor antagonists in addition to altering smooth muscle contraction, may have other actions on cellular dynamics (4).

Medical management of BPH is becoming an increasing viable alternative to surgical treatment (18). Hormonal manipulation is one strategy (19); a second is the search for drugs which block adrenergic receptors (20).

The ability of α_1–adrenergic blockers to inhibit prostatic contractions is the basis for their use in BPH. But the first generation of α_1–adrenoceptor antagonists used for the treatment of BPH was originally developed for the treatment of hypertension. All these drugs, while decreasing urinary flow resistance could also cause unwanted cardiovascular side effects due to their blood pressure lowering potency (4, 8). Therefore, there have been attempts to develop α_1–adrenoceptor antagonists having minimal hypotensive effect (12). Moreover, there also have been some reports of α_1–adrenoceptor antagonists decreasing baroreflex sensitivity. Sasso and O' Connor (21) reported depression of baroreflex sensitivity by prazosin (α_1–adrenoceptor antagonist) suggesting a plausible mechanism for the lack of reflex sympathetic outflow. Although several α_1–AR antagonists including terazosin show similar selectivity for prostate versus vascular tissue of human (8), terazosin is used widely for the treatment of BPH. The effects of terazosin on symptom scores and urinary flow rates in BPH have been

documented (1, 8, 14, 22) but its effect on baroreflex is still not known. Thus the present study was planned to investigate the effect of three different doses of terazosin on baroreflex sensitivity.

METHODS

Animals

The present study was conducted on 10 aged, healthy male mongrel dogs, older than one year of age (23) weighing between 10–15 kg. Animals were housed in experimental animal facility of Patel Chest Institute for quarantine as well as for acclimatization. Dogs were kept in a well ventilated room at ambient temperature ranging from 24°C±2°C. Necessary care was taken in handling of the animal for proper conditioning. The Indian National Science Academy's guidelines for the care and use of laboratory animals were followed.

Anaesthesia

The animals were anaesthetized with intravenous pentobarbitone sodium (35 mg/kg of body weight). The adequate anesthesia was indicated by disappearance of the corneal reflex in the animal. Later small doses of the anesthetic were administered intraveously as required.

Surgical procedures and measurements

The anaesthetized animal was placed in supine position, trachea was cannulated with a cannula and dogs were ventilated using a respiratory pump (Inco) at the rate of 25/min and with a tidal volume of 12 ml/kg to give a constant ventilation of 300 ml/kg/min. The ventilatory variables were adjusted for normal arterial pO_2, pCO_2 and pH before starting the cardiovascular measurements.

A polyethelene catheter was placed in descending aorta through a femoral artery for recording arterial blood pressure (B.P.) with a pressure trasducer (Statham P-23 Db). The pressure recording system was calibrated with the help of mercury manometer before each experiment. The femoral vein was cannulated for intravenous injection of saline and drugs.

The procedure for implanting catheter, for recording prostatic contraction, was followed as described earlier (24). The bladder was incised and a polyethylene catheter with a 2–3 ml capacity balloon tip was introduced through the bladder into the prostatic urethra. The balloon was filled with air and the catheter withdrawn until the balloon became lodged in the prostate, which was confirmed by mechanical pressure. The Balloon of the catheter in the prostatic urethra, when pressed by the prostatic contraction, the resultant change in the pressure was recorded as an index of prostatic contractility. Prostatic pressure and haemodynamic parameters were measured on a Polygraph (Lectromed, U.K.). Measurements were started 30 min after completion of surgical procedures. Following an hour of equilibration, a graded dose-response relationship to phenylephrine (1 to 16 µg/kg i.v.) was obtained on haemodynamic parameters, i.e. blood pressure and heart rate and intraurethral pressure, an index for prostatic contractility.

The α_1–adrenergic antagonist, terazosin was administered in three different doses [10 µg/kg, 100 µg/kg and 300 µg/kg] i.v. 15 minutes before construction of phenylephrine curves (constructed up to a maximum dose of 512 µg/kg in the presence of terazosin).

Statistical analysis

All data are presented as mean ± SEM and compared by analysis of variance (ANOVA). Post terazosin values were compared with control by paired t-test. Significance level was set at $P<0.05$.

RESULTS

Effect of terazosin on blood pressure

On injection of phenylephrine in progressive increasing doses of 1–16 µg/kg, a corresponding rise in systolic blood pressure (SBP) was observed (Fig. 1). The basal value of SBP was 137.50±6.7 mm Hg which was found to increase with progressive dose-strength of phenylephrine. Following the maximum dose of 16 µg/kg the SBP was recorded as 191.25±5.5 mm Hg. On injection of the first dose of terazosin (10 µg/kg), the SBP fell to 122.5±5 mm Hg. Subsequently, phenylephrine was injected in increasing doses from 1–32 µg/kg. However, the corresponding increase in SBP was significantly ($P<0.05$) less than the control value (Fig. 1). At a higher dose strength of phenylephrine (32 µg/kg), the maximum rise in SBP was recorded as 196.2±6.2 mm Hg. Consequent to terazosin injection in a strength of 100 µg/kg as the second dose, the SBP fell further to 103.75±7.4 mm Hg. The response to increasing doses of phenylephrine was found to be further attenuated (Fig. 1) and the SBP recorded with the maximum dose of 128 µg/kg phenylephrine, was 208.75±5.1 mm Hg. The third dose of terazosin, in a strength of 300 µg/kg, was associated with a decrease of SBP to 97.5±6.1 mm Hg. Following this dose, phenylephrine was injected in progressive strengths of 1–512 µg/kg, the rise of SBP recorded was significantly reduced after the injection of phenylephrine from the doses of 16 to 512 µg/kg (Fig. 1). The SBP recorded at a dose of 512 µg/kg was 238.75±6.5 mm Hg. Phenylephrine in progressive increasing doses of 1–16 µg/kg, produced a corresponding progressive rise in diastolic blood pressure (DBP) (Fig. 2). The basal value of DBP was 98.75±7 mm Hg which was found to increase with progressive dose-strength of

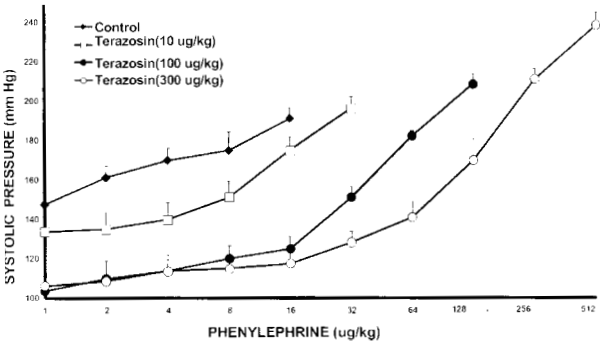

Fig. 1: Effects of intravenous administration of phenylephrine on systolic blood pressure (SBP) before and after the injection of three doses (10 µg/kg, 100 µg/kg and 300 µg/kg) of terazosin. In control (prior to administration of terazosin), the maximum dose of PE injected was 16 µg/kg.

SBP after individual dose of PE and post terazosin were compared with the respective control values (prior to terazosin). SBP values for the post terazosin observation were found to be significantly ($P<0.05$) reduced for all the doses of PE as compared with the control values. All values are mean±S.E.M obtained from 10 dogs.

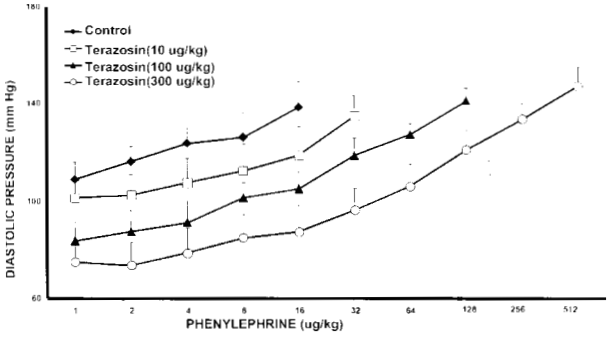

Fig. 2: Effects of intravenous administration of phenylephrine on diastolic blood pressure (DBP) before and after the injection of three doses (10 µg/kg, 100 µg/kg and 300 µg/kg) of terazosin. In control (prior to administration of terazosin), the maximum dose of PE injected was 16 µg/kg.

DBP after individual dose of PE and post terazosin were compared with the respective control values (prior to terazosin). DBP values for the post terazosin observation were found to be significantly ($P<0.05$) reduced for all the doses of PE as compared with the control values. All values are mean±S.E.M obtained from 10 dogs.

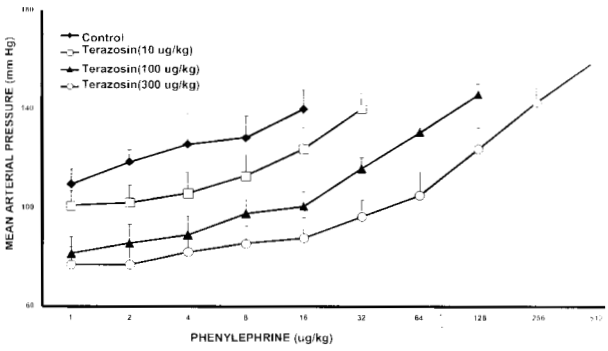

Fig. 3: Effects of intravenous administration of phenylephrine on mean arterial pressure (MAP) before and after the injection of three doses (10 µg/kg, 100 µg/kg and 300 µg/kg) of terazosin. In control (prior to administration of terazosin), the maximum dose of PE injected was 16 µg/kg.

MAP after individual dose of PE and post terazosin were compared with the respective control values (prior to terazosin). MAP values for the post terazosin observation were found to be significantly ($P<0.05$) reduced for all the doses of PE as compared with the control values. All values are mean±S.E.M obtained from 10 dogs.

phenylephrine. Following the maximum dose of 16 µg/kg the DBP increased to 138.75±10.4 mm Hg. On injection of the first dose of terazosin (10 µg/kg), the DBP fell to 92.5±6.2 mm Hg. Subsequently, phenylephrine was injected in increasing doses from 1–32 µg/kg. However, the corresponding increase in DBP was significantly ($P<0.05$) less than the control (Fig. 2). At a higher dose strength of phenylephrine (32 µg/kg), DBP rose to 135.0±8.4 mm Hg. Consequent to terazosin injection in a strength of 100 µg/kg as the second dose, the DBP fell further to 83.75±7.1 mm Hg. The response to increasing doses of phenylephrine was found to be further attenuated and the DBP with the maximum dose of 128 µg/kg phenylephrine, was 141.25±5.1 mm Hg. The third dose of terazosin, in a strength of 300 µg/kg, was associated with further fall in DBP to 70.0±4.3 mm Hg. Following this dose, with phenylephrine in progressive strengths of 5–512 µg/kg, the rise of DBP was further reduced (Fig. 2). The DBP at a dose of 512 µg/kg of phenylephrine was 147.50±7.7 mm Hg. Injection of phenylephrine in progressive increasing doses of 1–16 µg/kg produced a corresponding progressive rise in mean arterial pressure (MAP) (Fig. 3). The basal value of MAP was 100.5±5.7 mm Hg which was found to increase with progressive dose-strength of phenylephrine. Following the maximum dose of 16 µg/kg of phenylephrine, the MAP was 139.8±7.7 mm Hg. On injection of the first dose of terazosin (10 µg/kg), the MAP fell to 92.25±5.9 mm Hg. Subsequently, phenylephrine was injected in increasing doses from 1–32 µg/kg. However, the corresponding increase in MAP was significantly ($P<0.05$) less than control

values (Fig. 3). At a higher dose strength of phenylephrine (32 µg/kg), the maximum rise in MAP was 139.87±6.4 mm Hg. Consequent to terazosin injection in a strength of 100 µg/kg as the second dose, the MAP fell further to 81.37±6.5 mm Hg. The response to increasing doses of phenylephrine was found to be further attenuated and the MAP with the maximum dose of 128 µg/kg of phenylephrine was 145.87±4.3 mm Hg. The third dose of terazosin, in a strength of 300 µg/kg, was associated with a further fall in MAP to 71.25±2.1 mm Hg. Following this dose, phenylephrine was injected in progressive strengths of 1–512 µg/kg, however, the effect on rise of MAP was further reduced (Fig. 3). The MAP recorded at a dose of 512 µg/kg phenylephrine was 159.37±6 mm Hg.

Effect of terazosin on heart rate

The basal heart rate before injection of terazosin was 164±3 beats/min. On injection of 10 µg/kg of terazosin, it was 167±2 beats/min. Following injection of higher doses of terazosin, 100 µg/kg and 300 µg/kg, the heart rate was 173±1 and 181±4 beats/min respectively. Thus as expected, terazosin even in the higher doses did not produce any significant change in the basal heart.

Effect of terazosin on baroreflex

Arterial baroreceptor mediated regulation of arterial pressure (baroreflex) was examined by recording mean arterial pressure and heart rate (HR) relationship. Blood pressure was changed by injecting varying doses of phenylephrine and the

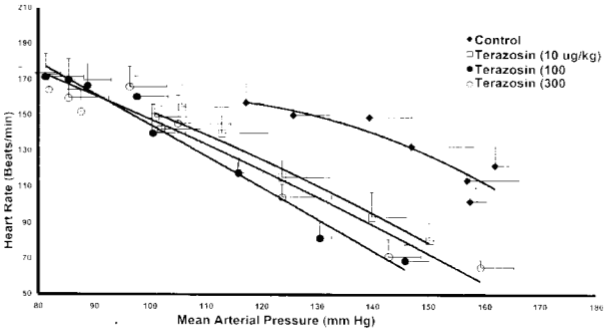

Fig. 4: Effects of terazosin in three doses (10 µg/kg, 100 µg/kg and 300 µg/kg) on baroreflex sensitivity. On intravenous administration of phenylephrine in progressive doses [1–512 µg/kg], there was a corresponding rise in control blood pressure and fall in heart rate.

In controls (prior to administration of terazosin), the maximum dose of PE injected was 16 µg/kg. MAP–HR curves were constructed by injecting progressive increasing doses of PE and recording subsequent changes in the heart rate.

Baroreflex sensitivity was calculated from MAP–HR curve (prior to administration of terazosin) and from post terazosin, MAP–HR curves. There was no significant difference between the control and post terazosin observations on baroreflex sensitivity. All values are mean±S.E.M obtained from 10 dogs.

corresponding changes in heart rate were recorded. Baroreflex sensitivity (Δ HR/Δ MAP) was calculated from the MAP–HR curves. Baroreflex sensitivity after injecting the three doses of terazosin (10 µg/kg, 100 µg/kg and 300 µg/kg) was compared with the baroreflex sensitivity values obtained before injecting terazosin (control). Baroreflex sensitivity calculated from the MAP–HR curve for the control was 1.53. Baroreflex sensitivity for 100 µg/kg of terazosin was 1.57 and for 100 and 300 µg/kg of terazosin, it was 1.70 and 1.50 respectively. There was no significant difference between the control and post-terazosin baroreflex sensitivity values (Fig. 4, Table I).

TABLE I: Baroreflex Sensitivity.

Treatment	*(Δ HR/Δ MAP) beats/min/mm Hg*
Control	1.53±0.32
Terazosin (10 µg/kg)	1.57±0.41
Terazosin (100 µg/kg)	1.70±0.59
Terazosin (300 µg/kg)	1.50±0.45

Effect of terazosin on prostatic pressure

On injection of phenylephrine in progressive increasing doses of 1–16 µg/kg, a corresponding progressive rise in prostatic pressure (P.P) was observed (Fig. 5). The basal value of P.P was taken as zero rise in the pressure of the balloon placed in the prostatic urethra. The pressure of the balloon was taken as an index for prostatic contractile state. There was a proportional increase in the P.P with increasing dose-strength of phenylephrine. Following the maximum dose of 16 µg/kg of phenylephrine the P.P was 4.5±0.6 mm Hg. EC_{50} (the dose of PE producing 50% of the maximum effect) for the control was 2.8 µg/kg. On injection of the first dose of terazosin (10 µg/kg), there was no effect on P.P. Subsequently, phenylephrine was injected in increasing doses from 1–32 µg/kg. However, the corresponding increase in P.P was significantly ($P<0.05$) less than the control values (Fig. 5). EC_{50} calculated for 10 µg/kg of terazosin was 16 µg/kg. At a higher dose strength of phenylephrine (32 µg/kg), maximum rise in P.P was 2.75±0.4 mm Hg. Consequent to terazosin injection in a strength of 100 µg/kg as the second dose, the effect of increasing doses of phenylephrine on P.P was further reduced after the injection of phenylephrine from the doses of 8 to 128 µg/kg (Fig 5), and the P.P recorded with the maximum dose of 128 µg/kg, was 2.87±0.5 mm Hg. EC_{50} calculated for this dose of terazosin was 48 µg/kg. The third dose of terazosin was injected in a strength of 300 µg/kg. Following this dose, phenylephrine was injected in progressive strengths of 1–512 µg/kg. The effect on the rise of P.P was significantly reduced after the injection of phenylephrine in doses of 16 to 512 µg/kg (Fig. 5). The P.P recorded at a dose of 512 µg/kg was 3.37±1 mm Hg. EC_{50} calculated for 300 µg/kg of terazosin was 180 µg/kg.

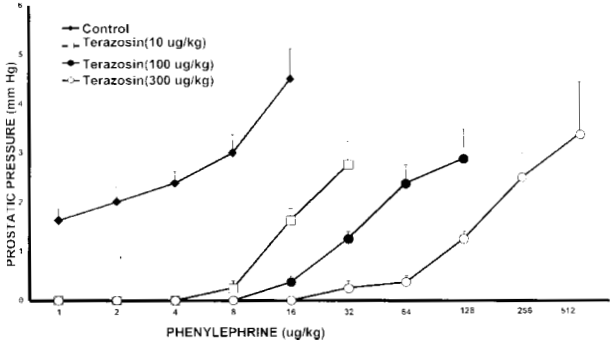

Fig. 5: Effects of terazosin in three doses (10 µg/kg, 100 µg/kg and 300 µg/kg) on increase in prostatic pressure (PP) by phenylephrine. On intravenous administration of phenylephrine in progressive doses [1–512 µg/kg], there was a dose-related rise in the prostatic pressure. In controls (prior to administration of terazosin), the maximum dose of PE injected was 16 µg/kg. The PP after individual dose of PE and post terazosin were compared with the respective control values (prior to terazosin). The PP values for the post terazosin observation were found to be significantly ($P<0.05$) reduced for all the doses of PE as compared with the control values. All values are mean±S.E.M obtained for 10 days.

DISCUSSION

This study was performed to study the effects of terazosin on baroreflex while inhibiting adrenergic receptor mediated prostatic contractions in a dose dependent manner.

In our study, dog was taken as an animal model for evaluation of urogenital α-adrenoceptor antagonistic activity. The

first demonstration of the contractile response of prostatic tissue to α-adrenoceptor activation was performed using rat prostate (25) but now this tissue is not commonly used as a model for prostate α_1-adrenoceptor, owing to the low density of stromal smooth muscle relative to prostate glands from other species, including humans. The canine prostate has been well characterized in vitro. The sensitivities of canine and human prostate to α_1-adrenoceptor agonists and antagonists appear to be similar (26, 27). As observed for human prostate, radioligand binding assays detected the presence of both α_1-and α_2-adrenoceptors in canine prostate, although the functional response to α-adrenoceptor agonists appears to be mediated entirely by α_1-adrenoceptor.

Tone in the canine prostatic urethra can be measured either via a balloon catheter or by determination of urethral pressure profiles by a procedure similar to that used in human. In our study, we used the balloon catheter technique, as we wanted catheter to be retained in the prostatic urethra, in order to construct the graded dose-response relationship to phenylephrine. As expected there was a dose-dependent rise in the blood pressure on intravenous administration of phenylephrine, both before and after the treatment with terazosin. However, the concentration response curves, between dose of phenylephrine and blood pressure, shifted towards right corresponding to the amount of terazosin injected. This shift was related to the initial fall in the blood pressure on injection of terazosin but the slopes of the curves did not show any significant difference from the control curve suggesting that the sensitivity to the α-adrenoceptor agonist was not affected by even the highest dose of terazosin (300 μg/kg) used in the present study.

Rise in the blood pressure by phenylephrine produced a corresponding fall in the heart rate under control condition as well as after injection of terazosin in varying doses. This inverse relationship between the blood pressure and the heart rate suggests an operative baroreflex regulatory mechanism to restore the normal blood pressure. Terazosin did not produce any significant change in the basal heart rate but it shifted the mean arterial pressure-heart rate curves towards the left of the control curve. Terazosin did not produce any significant change in the baroreflex sensitivity at any of the three doses of the blocker used.

Dose-dependent rise in prostatic contraction by α-adrenoceptor agonist was drastically inhibited by the terazosin. Terazosin shifted the dose-response curves towards the right of the control curve with an increase in the threshold dose of phenylephrine to increasing prostatic contraction. The increase in threshold dose of phenylephrine was proportional to the amount of terazosin injected. Significant inhibition of the α-adrenergic mediated prostatic contraction even by the smallest dose of terazosin (10 μg/kg) makes it a drug of choice for the symptomatic treatment of benign prostate hypertrophy. This dose of terazosin dose not cause any adverse effect on the cardiovascular system and even the highest dose of the drug did not impair the neural regulation of arterial blood pressure through arterial baroreceptors.

In conclusion, terazosin can be used as a potent drug for the symptomatic treatment of benign prostate hypertrophy without any adverse effect on the cardiovascular system.

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