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A REVIEW OF: SUSTAINED RELEASE TABLET OF DOXAZOSIN MESYLATE FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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Abstract:

Evidence from various studies has shown that even a very small reduction in the blood pressure explains the majority of benefits in cardiovascular outcomes. Although doxazosin is a relatively old drug, it is a very effective add-on therapeutic agent. It has been used in a variety of clinical trials, including different groups of hypertensive patients such as diabetics, the elderly, patients with benign prostatic hyperplasia or hypercholesterolaemia, the obese or Afro-Americans and in combination with all major groups of antihypertensive drugs such as: calcium channel antagonists, diuretics, beta-adrenoreceptor antagonists, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers. The purpose of this article is to review the role of doxazosin in the current treatment of hypertension. English-language reports published in 1986 - 2007 were retrieved. In these studies doxazosin in either standard or extended-release formulation was added as a second- or third-line agent. The two formulations of doxazosin, although chemically identical, appear to differ in some other effects. A large proportion of patients demonstrated a favorable blood pressure response with relatively few treatment-associated side effects showing that this drug appears to be a valuable add-on antihypertensive treatment option. Doxazosin reduces blood pressure and additionally influences other risk factors of coronary heart disease. However, it should be clearly stated that the clinical role of 'beyond blood pressure' effects of doxazosin are largely undetermined.

Key words: *Doxazosin Mesylate, Sustained release tablet, High blood pressure and benign prostatic hyperplasia.*

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INTRODUCTION:

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form[1,2] . Advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[3] . Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems[4] . Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers[5]. One of the interesting results of pharmaceutical research is the fact that absorption rate of a drug can be decreased by reducing its rate of release from the dosage form.

The product so formulated are designated as sustained action, sustained release, delayed action, prolonged action, depot, respiratory, retarded release and timed release medication.[6,7] Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels.[8]

Sustained release concept: - Sustained release, sustained action, prolong action, controlled release, extended action, depot are terms used to identify drug delivery systems that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administer this period is measured in hours while in the case of injectables this period varies from days to months.

Parameters for drug to be formulated in sustained release dosage form:

Physicochemical parameters for drug selection.

1. Molecular weight/size < 1000 Daltons.
2. Solubility > 0.1 mg/ml for pH 1 to pH 7.8.
3. Apparent partition coefficient High.
4. Absorption mechanism Diffusion.
5. General absorbability from all GI segments.
6. Release should not be influenced by pH and enzymes.

Pharmacokinetic parameters for drug selection

1. Elimination half-life preferably between 2 to 8 hrs
2. Total clearance should not be dose dependent
3. Elimination rate constant required for design
4. Apparent volume of distribution (Vd) The larger Vd and MEC, the larger will be the required dose size
5. Absolute bioavailability should be 75% or more
6. Intrinsic absorption rate must be greater than release rate
7. Therapeutic concentration Css The lower Css and smaller Vd, the loss among of drug required.
8. Toxic concentration Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Approaches To Sustain Release Drug Delivery System

1. Dissolution controlled release systems.

2. Diffusion controlled release systems.
3. Dissolution and diffusion-controlled release systems.
4. Ion exchange resin- drug complexes.
5. pH dependent formulation.
6. Osmotic pressure-controlled systems.

1. Dissolution controlled release systems
These systems are easy to formulate. Drug which are formulated using system have slow dissolution rate, produce slow dissolving forms with gastric intestinal fluids and the drugs which are having high aqueous solubility and dissolution rate. Dissolution controlled release system can be classified into two techniques

A. Matrix dissolution controlled release system
Matrix dissolution system is known as monolithic because the drug present in the matrix is completely dissolved in the medium which controls the drug release. They are mostly made of waxes like beeswax, carnauba wax, hydrogenated castor oil, etc. and play important role to control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate The drug release generally follows first order kinetics from such matrices system.

B. Reservoir dissolution-controlled release system
In reservoir system, the drug particles are coated or encapsulated with one of the several microencapsulation techniques using slowly dissolving materials like cellulose, polyethylene glycol and waxes. This unit can be encapsulated in capsules or may be compressed into tablets Solubility and thickness of the coating play important role in dissolution rate of drug.

2. Diffusion controlled release systems
In diffusion release models, the diffusion of dissolved drug through a polymeric membrane is a rate limiting step. In this system, the drug release rate never follows zero-order kinetics, because the diffusion path length increases with time as the insoluble matrix is drug depleted. The mechanism of diffusion process shows the movement of drug molecules from a region of a higher concentration to region of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.J = -D dc/dx where, J = flux of the drug across a membrane in the direction of decreasing conc.,D = Diffusion coefficient of the drug, and dc /dx = Change in the concentration of the drug in the membranewhereas when drug present in a water insoluble membrane, it must diffuse through the membrane.The drug release rate dm/ dt is given by dm = ADKΔ C/dt L where, A = Area. K = Partition coefficient of drug between the membrane and drug core. L = Diffusion path length (i.e. thickness of coat). ΔC=Concentration difference across the membrane.

3. Dissolution and diffusion-controlled release systems
In this kind of system, the drug is enclosed in a membrane which is partially water soluble. The dissolution of the membrane take place due to which pores are formed and these pores allows aqueous medium to enter in the membrane. This results in the dissolution of the drug in membrane followed by the diffusion of the dissolved drug from the system. Example of such coating is combination of ethyl cellulose with PVP or methyl cellulose.

4. Ion exchange resin- drug complexes:
Resins are the materials which are insoluble in water. Resin contains anionic groups such as amino or quaternary ammonium groups and cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the chain. A drug–resin complex is formed by prolonged exposure of drug to the resin. The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na+ and Cl- present in gastrointestinal tract.

Resin+ – Drug– + Cl– ---------- > >> resin+ Cl– + Drug–
Where x- is Cl- conversely

Resin– – Drug+ + Na+ ---------- > >> resin– Na+ + Drug
Water insoluble cross linked polymer compounds are used for this system.

5. PH dependent formulation
Some drugs on dissolution and absorption in GIT, changes the pH present in the gastrointestinal tract, so dosage forms are formulated using sufficient amount of buffering agent like salt of phosphoric, citric or tartaric acids. These salts adjust the pH to the desired value when dosage form move across the gastrointestinal tract. Permeable coating agents are used to coat the drug and buffer present in the dosage form, which allows the aqueous medium to enter in it and prevents the dispersion of the tablets.

6. Osmotic pressure controlled systems

These types of system are also known as oros, which follows the mechanism of osmotic pressure where the drug is released at constant zero order rate. The reservoir is made up of the drug and osmotic agent like mannitol or KCl, which is surrounded by semi permeable membrane. A small orifice is present in the dosage form, which allows the entry of water in the reservoir and helps the dissolved drug to pumped out at the determined rate due to osmotic pressure. The release of the drug from the reservoir is unaffected by the conditions of the GIT. The release of drug is depended on factors like size of orifice, thickness of semi permeable membrane, permeability of membrane, osmotic properties of core and stability of the drug.[9]

Objectives of oral sustained released dosage form

• To maintain the concentration of drug at constant level for a desired period of time.
• To reduce the frequency of doses administrated as compared to conventional dosage form
• It should deliver active entity directly to site of action, minimizing or eliminating side effects.
• This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.
• The safety margin of potent drugs can be increased.
• Incidence of both local and systemic adverse side effects can be reduced in sensitive patient [10-14].

Commercial / Industrial Advantages

• Illustration of innovative /technological
• Leadership • Product life-cycle extension
• Product differentiation
• Market expansion
• Patent extension [15]

Challenges to sustained release drug delivery

1. Biocompatibility
2. Cost of formulation, preparation and processing
3. Fate of controlled release system if not biodegradable
4. Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers etc [16].

Advantages of SRDDS

Following are some advantages of SRDDS: [17-21]

Reduction in frequency of drug administration

- Improved patient compliance
- Reduction in drug level fluctuation in blood
- Reduction in total drug usage when compared with conventional therapy
- Reduction in drug accumulation with chronic therapy
- Reduction in drug toxicity (local/systemic)
- Stabilization of medical condition (because of more uniform drug levels)
- Improvement in bioavailability of some drugs because of spatial control
- Economical to the health care providers and the patient

Disadvantages of SRDDS [22-24]

Following are some disadvantages of SRDDS:

- Delay in onset of drug action.
- Possibility of dose dumping in the case of a poor formulation strategy.
- Increased potential for first pass metabolism
- Greater dependence on GI residence time of dosage form.
- Possibility of less accurate dose adjustment in some cases.
- Cost per unit dose is higher when compared with conventional doses.
- Not all drugs are suitable for formulating into ER dosage form.
- Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, Ph dependent stability etc.
- Poor In vitro – In vivo correlation.
- Retrieval of drug is difficult in case of toxicity, poisoning (or) hypersentivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strength.

MATERIAL AND METHODS

Study Design

An open-label, noncomparative, multicenter study was conducted. The participants were general practitioners from Spain. The patients were recruited from primary care. The health care authorities were notified of the study and it was carried out in agreement with the pharmacovigilance guidelines in Spain and the ethical guidelines of the Helsinki Declaration.

Patients

The patients included in the study were males >40 years, with hypertension of >1 year's duration that has been controlled (diastolic blood pressure [DBP] ≤95 mm Hg) with a single antihypertensive drug for at least 6 months prior to inclusion and who came to consultation due to symptomatology or prostatic

syndrome (I-PSS questionnaire ≤7 points). Patients with a history of syncope or orthostatic hypotension, dizziness or vertigo, and severe hypertension or prostate cancer were excluded. The degree of control (≤95 mm Hg DBP) would not be considered adequate according to recent guidelines.

Treatment was initiated with 1 mg/day of doxazosin taken orally for the first 2 weeks, titrated at 2-week intervals to 2 mg/day and 4 mg/day, which is the usual dosage for the treatment of prostatic syndrome. The maximum dosage of 4 mg/day was unchanged throughout 14 weeks of follow-up unless there were side effects that the patient could not tolerate (postural hypotension, dizziness, or vertigo). In this situation, the dosage of doxazosin or of the other antihypertensive agents was adjusted.

Methods

Blood pressure and heart rate were determined three times at each visit, and the mean of the readings was considered the visit blood pressure. The blood pressure was measured whenever possible by the same individual and using the same arm of the patient, following the recommendations of the British Society of Hypertension.

To quantify the symptoms of the patients, we used the I-PSS and Quality of Life Assessment developed by the American Urology Association Evaluation Committee, 18 translated and validated in Spanish, 19 which the patient filled out during the baseline visit and after 14 weeks of treatment. This questionnaire is made up of seven questions on symptoms, with six possible answers scored from 0–5, which indicate increasing severity of each symptom, so that the minimum score is zero (asymptomatic) and the maximum 35 (very symptomatic). Scores >7 and <19 corresponded to patients with moderate symptoms and scores from 20–35 indicated severe symptoms. Quality of life was scored on the basis of only one question: how the patient would feel if he had to spend the rest of his life with the symptoms he was currently suffering. This question had seven possible answers: from zero (very good) to six (very bad). The score obtained is independent from that of the I-PSS although the assessment of the quality of life is always used together with the I-PSS.

All adverse events were recorded, including the date of occurrence, duration, intensity (mild, moderate, severe), seriousness, likelihood of association with the study drug (yes, no, uncertain/unknown), and their resolution.

Statistics

The sample comprised 2363 patients. It was calculated according to the percentage of adverse effects related to the reduction of blood pressure when doxazosin was added to the previous antihypertensive drug at the dosage recommended for the of prostatism or prostatic syndrome.

The side effects produced by blood pressure reduction may differ in both nature and intensity. We used syncope, the most severe adverse effect that can occur with the reduction of blood pressure, to calculate the sample size. The syncope rate in patients treated with any antihypertensive drug has been established as 0.5%–1.0%, with an average value of 0.7% for doxazosin in the clinical trials.

We assumed that a syncope rate greater than twice that documented in the clinical experience (1.4%; odds ratio, 2) after treatment with doxazosin, would be enough to rule out the simultaneous use of doxazosin and another antihypertensive drug in the patients selected for this study.

Descriptive analyses were performed and means with standard deviations and proportions were estimated where appropriate.

Group comparisons were made with analysis of variance. Relations between variables were determined with the Pearson correlation. Two sided p values at 0.05 were taken as statistically significant. Separate analyses were performed for subgroups according to age and initial antihypertensive treatment.[25-26]

DOXAZOSIN MESYLATE

Description

Doxazosin Mesylate is the mesylate salt form of doxazosin, a quinazoline compound with smooth muscle relaxing activity. Doxazosin mesylate selectively antagonizes alpha-1-adrenergic receptors in smooth muscle of the bladder neck and prostate, thereby relaxing the smooth muscle and decreasing the obstruction and urethral resistance seen with benign prostate hyperplasia (BPH). This may improve BPH symptoms. This agent also blocks alpha-1-adrenergic receptors in peripheral vascular smooth muscle, which leads to vasodilatation and a subsequent decrease in peripheral vascular resistance. Common side effects include dizziness, sleepiness, swelling, nausea, shortness of breath, and abdominal pain. Severe side effects may include low blood pressure with standing, an irregular heart beat, and

priapism. It is a selective α1-adrenergic blocker in the quinazoline class of compounds.

Doxazosin was patented in 1977 and came into medical use in 1988. It is available as a generic medication. In 2022, it was the 180th most commonly prescribed medication in the United States, with more than 2 million prescriptions.

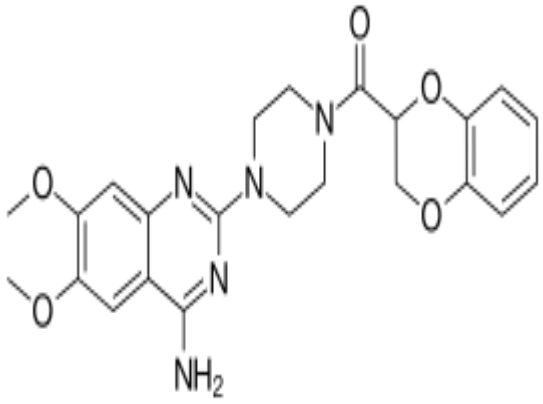
History

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study stopped its arm of the trial looking at alpha blockers, because doxazosin was less effective than a simple diuretic, and because patients on doxazosin had a 25% higher rate of cardiovascular disease and twice the rate of congestive heart failure as patients on diuretics. Pfizer, aware of the results before publication, launched a marketing campaign in early 2000, and sales were largely unaffected, despite the dangers highlighted by the study. The decision to stop the trial was controversial because the higher rate of heart failure (HF) in the doxazosin group could have been caused by misdiagnosis due to fluid retention from the medication, or because patients with existing HF stopped their diuretic treatment to switch to doxazosin. However, in the later ASCOT trial, where doxazosin was used as a third-line treatment, there was no increase in HF risk.

Synonym :
Methanesulfonate

Drug category : Antihypertensive Agents

Structure :



Chemical name/ Nomenclature / IUPAC Name :
2-[4-(2,3-dihydro-1,4-benzodioxine-2-carbonyl)piperazin-1-yl]-6,7-dimethoxy-3,4-dihydroquinazolin-4-imine; methanesulfonic acid

Molecular Formula : $C_{24}H_{29}N_5O_8S$

Molecular Weight : 547.58 gm/mole.

Official Pharmacopoeia : USP

PHYSICOCHEMICAL PROPERTIES:

Description (Physical State): Solid

Solubility: Water Solubility 0.79 mg/mL and Freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8 percent at 25 °C), and very slighlty soluble in acetone and methylene chloride.

Dosage: Tablet

Melting point: 289-290 °C

pKa(strongest acidic): 12.67

Log P: 1.49

PHARMACOKINETIC PROPERTIES:

Bioavailability : 65 %

Half-life : 22 hrs

Absorption : 65%

Protein binding : 98 %

Metabolism : Liver

Adverse effects/Side effects :

Common side effects may include:

- Low blood pressure, dizziness;
- Drowsiness
- Headache or
- Feeling weak or tired
- A light-headed feeling, like you might pass out
- Severe ongoing stomach pain or bloating
- New or worsening chest pain
- Trouble breathing

PHARMACODYNAMICS:

Mechanism of action:

Doxazosin acts by inhibiting the postsynaptic alpha(1)-adrenoceptors on vascular smooth muscle. This inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation.

Therapeutic efficacy/ Indications:

High blood pressure

Doxazosin is usually added to other antihypertensive therapy such as calcium channel antagonists, diuretics, beta-adrenoreceptor antagonists, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers.

Doxazosin is generally considered to be safe, well tolerated and effective as an add-on (adjunctive) antihypertensive drug.

Like other alpha-1 receptor antagonists, it has a role in the peri-operative management of pheochromocytoma.

Benign prostatic hyperplasia

Doxazosin is considered to be effective in reducing urinary symptom scores and improving peak urinary

flow in men with benign prostatic hyperplasia.[10] The bladder neck is densely packed with alpha-1 receptors.

PTSD nightmares and flashbacks
Sympatholytic drugs, including prazosin and doxazosin, are used for nightmares and flashbacks in posttraumatic stress disorder (PTSD). Doxazosin is very well tolerated for this constellation of symptoms. Given its long half-life, doxazosin lasts much longer than prazosin. While prazosin is dosed up to 4 times daily, doxazosin is generally dosed only once daily (at night). Both are alpha-1 antagonists. Other sympatholytic drugs include clonidine and guanfacine, which are alpha-2 agonists; they are not in the same exact class as doxazosin and prazosin.

INTERACTIONS:
Drug interactions:
- The metabolism of Doxazosin can be decreased when combined with Acetazolamide.
- The risk or severity of adverse effects can be increased when Doxazosin is combined with Acetylcholine.
- The metabolism of Doxazosin can be decreased when combined with Albendazole.
- The risk or severity of adverse effects can be increased when Benazepril is combined with Doxazosin.
- The risk or severity of adverse effects can be increased when Bendroflumethiazide is combined with Doxazosin.

Food interactions:
- ✓ Avoid alcohol.
- ✓ Avoid natural licorice.
- ✓ Take without regard to meals.

Dosing information
Usual Adult Dose for Hypertension:
Initial dose: 1 mg orally once a day.
Maintenance dose: 1 to 16 mg orally once a day.
Usual Adult Dose for Benign Prostatic Hyperplasia:
Initial dose:
Immediate-release: 1 mg orally once a day.
Extended-release: 4 mg orally once a day with breakfast
Maintenance dose:
Immediate-release: 1 to 8 mg orally once a day.
Extended-release: 4 to 8 mg orally once a day with breakfast. Depending on the patient's symptomatic response and tolerability, the dose may be increased to 8 mg (the maximum recommended dose). The recommended titration interval is 3 to 4 weeks.

If switching from immediate-release doxazosin tablets to extended-release tablets, therapy should be initiated with the lowest dose (4 mg once daily). Prior to starting therapy with doxazosin extended-release tablets, the final evening dose of immediate-release tablets should not be taken. If doxazosin extended-release tablets are discontinued for several days, therapy should be restarted using the 4 mg once daily dose.

Usual Geriatric Dose for Hypertension:
Initial dose: 0.5 mg orally once a day.

Warnings
Doxazosin can affect your pupils during cataract surgery. Tell your eye surgeon ahead of time that you are using doxazosin. Do not stop using this medicine before surgery unless your surgeon tells you.

You should not use this medication if you are allergic to doxazosin or similar medicines such as alfuzosin (Uroxatral), prazosin (Minipress), silodosin (Rapaflo), tamsulosin (Flomax), or terazosin (Hytrin). Doxazosin may cause dizziness or fainting, especially when you first start taking it or when you start taking it again. Be careful if you drive or do anything that requires you to be alert. Avoid standing for long periods of time or becoming overheated during exercise and in hot weather. Avoid getting up too fast from a sitting or lying position, or you may feel dizzy.

Tell your doctor about all other medications you use, especially other blood pressure medications including diuretics (water pills).

DRUG FORMULATION:

S.No	Drug name	Label Claim	Brand name	Company
1	Doxazosin mesylate	4 mg	Cardura	Pfizer
2	Doxazosin mesylate	4 mg	Cardura-XL	Pfizer
3	Doxazosin mesylate	1 mg	Doxacard	CIPLA

DISEASE INTRODUCTION TO BE TREAT DOXAZOSIN

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH), also called prostate enlargement, is a noncancerous increase in size of the prostate gland. Symptoms may include frequent urination, trouble starting to urinate, weak stream, inability to urinate, or loss of bladder control. Complications can include urinary tract infections, bladder stones, and chronic kidney problems.

The cause is unclear. Risk factors include a family history, obesity, type 2 diabetes, not enough exercise, and erectile dysfunction. Medications like pseudoephedrine, anticholinergics, and calcium channel blockers may worsen symptoms. The underlying mechanism involves the prostate pressing on the urethra and thereby making it difficult to pass urine out of the bladder. Diagnosis is typically based on symptoms and examination after ruling out other possible causes.

Treatment options include lifestyle changes, medications, a number of procedures, and surgery. In those with mild symptoms, weight loss, decreasing caffeine intake, and exercise are recommended, although the quality of the evidence for exercise is low. In those with more significant symptoms, medications may include alpha blockers such as terazosin or 5α-reductase inhibitors such as finasteride. Surgical removal of part of the prostate may be carried out in those who do not improve with other measures. Some herbal medicines that have been studied, such as saw palmetto, have not been shown to help. Other herbal medicines somewhat effective at improving urine flow include beta-sitosterol from Hypoxis rooperi (African star grass), pygeum (extracted from the bark of Prunus africana), pumpkin seeds (Cucurbita pepo), and stinging nettle (Urtica dioica) root.

As of 2019, about 94 million men aged 40 years and older are affected globally. BPH typically begins after the age of 40. The prevalence of clinically diagnosed BPH peaks at 24% in men aged 75–79 years. Based on autopsy studies, half of males aged 50 and over are affected, and this figure climbs to 80% after the age of 80. Although prostate specific antigen levels may be elevated in males with BPH, the condition does not increase the risk of prostate cancer.

Signs and symptoms

BPH is the most common cause of lower urinary tract symptoms (LUTS), which are divided into storage, voiding, and symptoms which occur after urination. Storage symptoms include the need to urinate frequently, waking at night to urinate, urgency (compelling need to void that cannot be deferred), involuntary urination, including involuntary urination at night, or urge incontinence (urine leak following a strong sudden need to urinate). Voiding symptoms include urinary hesitancy (a delay between trying to urinate and the flow actually beginning), intermittency (not continuous), involuntary interruption of voiding, weak urinary stream, straining to void, a sensation of incomplete emptying, and uncontrollable leaking after the end of urination. These symptoms may be accompanied by bladder pain or pain while urinating, called dysuria.

Bladder outlet obstruction (BOO) can be caused by BPH. Symptoms are abdominal pain, a continuous feeling of a full bladder, frequent urination, acute urinary retention (inability to urinate), pain during urination (dysuria), problems starting urination (urinary hesitancy), slow urine flow, starting and stopping (urinary intermittency), and nocturia.

CAUSES

Hormones

Most experts consider androgens (testosterone and related hormones) to play a permissive role in the development of BPH. This means that androgens must be present for BPH to occur, but do not necessarily directly cause the condition. This is supported by evidence suggesting that castrated boys do not develop BPH when they age. In a study of 26 eunuchs from the palace of the Qing dynasty still living in Beijing in 1960, the prostate could not be felt in 81% of the studied eunuchs. The average time since castration was 54 years (range, 41–65 years). On the other hand, some studies suggest that administering exogenous testosterone is not associated with a significant increase in the risk of BPH symptoms, so the role of testosterone in prostate cancer and BPH is still unclear. Further randomized controlled trials with more participants are needed to quantify any risk of giving exogenous testosterone.

Dihydrotestosterone (DHT), a metabolite of testosterone, is a critical mediator of prostatic growth. DHT is synthesized in the prostate from circulating testosterone by the action of the enzyme 5α-reductase, type 2. DHT can act in an autocrine fashion on the stromal cells or in paracrine fashion by diffusing into nearby epithelial cells. In both of these

cell types, DHT binds to nuclear androgen receptors and signals the transcription of growth factors that are mitogenic to the epithelial and stromal cells. DHT is ten times more potent than testosterone because it dissociates from the androgen receptor more slowly. The importance of DHT in causing nodular hyperplasia is supported by clinical observations in which an inhibitor of 5α-reductase such as finasteride is given to men with this condition. Therapy with a 5α-reductase inhibitor markedly reduces the DHT content of the prostate and, in turn, reduces prostate volume and BPH symptoms.

Testosterone promotes prostate cell proliferation, but relatively low levels of serum testosterone are found in patients with BPH. One small study has shown that medical castration lowers the serum and prostate hormone levels unevenly, having less effect on testosterone and dihydrotestosterone levels in the prostate.

Diet

Studies indicate that dietary patterns may affect development of BPH, but further research is needed to clarify any important relationship.[38] Studies from China suggest that greater protein intake may be a factor in development of BPH. Men older than 60 in rural areas had very low rates of clinical BPH, while men living in cities and consuming more animal protein had a higher incidence. On the other hand, a study in Japanese-American men in Hawaii found a strong negative association with alcohol intake, but a weak positive association with beef intake.[41] In a large prospective cohort study in the US (the Health Professionals Follow-up Study), investigators reported modest associations between BPH (men with strong symptoms of BPH or surgically confirmed BPH) and total energy and protein, but not fat intake. There is also epidemiological evidence linking BPH with metabolic syndrome (concurrent obesity, impaired glucose metabolism and diabetes, high triglyceride levels, high levels of low-density cholesterol, and hypertension).

Pathophysiology

As men age, the enzymes aromatase and 5-alpha reductase increase in activity. These enzymes are responsible for converting androgen hormones into estrogen and dihydrotestosterone, respectively. This metabolism of androgen hormones leads to a decrease in testosterone but increased levels of DHT and estrogen.

Both the glandular epithelial cells and the stromal cells (including muscular fibers) undergo hyperplasia in BPH. Most sources agree that of the two tissues, stromal hyperplasia predominates, but the exact ratio of the two is unclear.

Diagnosis

The clinical diagnosis of BPH is based on a history of LUTS (lower urinary tract symptoms), a digital rectal exam, and exclusion of other causes of similar signs and symptoms. The degree of LUTS does not necessarily correspond to the size of the prostate. An enlarged prostate gland on rectal examination that is symmetric and smooth supports a diagnosis of BPH. However, if the prostate gland feels asymmetrical, firm, or nodular, this raises concern for prostate cancer.

Validated questionnaires such as the American Urological Association Symptom Index (AUA-SI), the International Prostate Symptom Score (I-PSS), and more recently the UWIN score (urgency, weak stream, incomplete emptying, and nocturia) are useful aids to making the diagnosis of BPH and quantifying the severity of symptoms.

HYPERTENSION

Hypertension, also known as high blood pressure, is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms itself. It is, however, a major risk factor for stroke, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia. Hypertension is a major cause of premature death worldwide.

High blood pressure is classified as primary (essential) hypertension or secondary hypertension. About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors. Lifestyle factors that increase the risk include excess salt in the diet, excess body weight, smoking, physical inactivity and alcohol use. The remaining 5–10% of cases are categorized as secondary hypertension, defined as high blood pressure due to a clearly identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.

Signs and symptoms

Hypertension is rarely accompanied by symptoms. Half of all people with hypertension are unaware that

they have it. Hypertension is usually identified as part of health screening or when seeking healthcare for an unrelated problem.

Some people with high blood pressure report headaches, as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes. These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.

Long-standing untreated hypertension can cause organ damage with signs such as changes in the optic fundus seen by ophthalmoscopy. The severity of hypertensive retinopathy correlates roughly with the duration or the severity of the hypertension. Other hypertension-caused organ damage include chronic kidney disease and thickening of the heart muscle.

Doxazosin mesylate is the most commonly prescribed therapy for patients with High blood pressure, Benign prostatic hyperplasia and PTSD nightmares and flashbacks. It has a good safety profile and is associated with low cost.

This study shows that adding doxazosin to the treatment of hypertensive patients with BPH who have been receiving antihypertensive single-drug treatment significantly reduces the prostatic symptomatology.

The absence of significant blood pressure reduction in patients with controlled blood pressure has been documented in other studies performed in normotensive patients with BPH. According to the authors, it seems that doxazosin would exert its antihypertensive effect only when peripheral vascular resistance is increased. Other European studies have demonstrated that the blood pressure reductions obtained with doxazosin in normotensive patients do not differ from those obtained with a placebo.

The side effects manifested by our patients were generally mild, except for syncope, which coincides with the studies previously reported.

As has been demonstrated by other authors, there were no differences in terms of the type of adverse effects and the antihypertensive drugs used before the introduction of doxazosin. In our study, we found a larger antihypertensive effect when doxazosin was combined with a diuretic or β blocker than when it was added to an ACE inhibitor or calcium antagonist. Side effects tended to occur early after onset of treatment with doxazosin. The differences in blood pressures with the different doxazosin combinations were larger after the patient had remained in treatment for at least 2 months, at a dosage of 2 mg/day or 4 mg/day, but not after 1 month at 1 mg/day. Therefore, it appears that side effects of the drug mainly result from the first dosage.[27-30]

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