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Terazosin and neuroprotection

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ABSTRACT

Terazosin (TZ) is a medication approved by the Food and Drug Administration (FDA) for use in the treatment of hypertension, as it lowers blood pressure. However, it was eventually discovered to be beneficial in the treatment of benign prostatic hyperplasia, and it was used to treat this disease as well. In addition to these two fields, the effects of TZ on neurodegenerative disorders are still unknown. Neurodegenerative disorders are caused by the loss of neurons. Their loss can also lead to the formation of diseases such as Parkinson's disease (PD), Alzheimer's disease, and Huntington's disease. The body uses the neuroprotection system to prevent certain disorders. In neurodegenerative disorders, it is thought that the combination and precise use of TZ and neuroprotection may have positive outcomes. The effects of TZ on PD are currently being studied.

Keywords: Benign prostatic hyperplasia, neurodegenerative diseases, neuroprotection, terazosin.

Terazosin (TZ) is a selective alpha-1 antagonist easily soluble in water, used by mild to moderate hypertension patients. It was approved by the Food and Drug Administration (FDA) in 1993 for the treatment of benign prostatic hyperplasia (BPH).[1,2] Benign prostatic hyperplasia is the abnormal growth of the prostate gland. Clinically, this condition manifests itself with lower urinary tract symptoms (LUTS).[3] The disease affects many men worldwide, and the number of affected individuals has increased to more than 210 million since 2010.[4] Benign prostatic hyperplasia affects 50% of men over the age of 50 and 80% of men over the age of 80, according to the data published in 2019.[5] The research on BPH goes back a long way and the cause of the disease was linked to age and the presence of testosterone in late 1800s.[6] When looking at its pathophysiology, sex hormones have been linked to various causes such as inflammation, neurotransmitters, and microorganisms.[7] The prostate is an organ found in males and consists of 20 to 40% smooth muscle.[8] The contraction properties of the prostatic smooth muscles were observed to be mediated by the alpha-1 adrenoceptor. Therefore, TZ was thought to be capable of treating this disease, and the studies showed it to be quick and effective as BPH patients' possibility of surgery was minimized by the treatment.[8] Alpha antagonists are the first stage of medical treatment, and contractions of the prostatic muscles are affected by alpha-1 adrenoreceptors.[9] Recently, it has been observed that the progression of Parkinson's disease (PD) can be slowed by TZ in addition to hypertension and BPH.[10] The positive effects were observed in rats with sepsis and PD, and this development has become a new hope.

Terazosin, first approved for hypertension treatment in 1987, was approved in 1993 as a treatment for LUTS, which is related to BPH.[11] Terazosin is also the second alpha-1 antagonist approved for use in the United States.[12] It is a treatment option for PD, as well as BPH, and almost four million prescriptions are filled

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every year.[13] Terazosin is found in tablets or capsules of 2.5 or 10 mg and is usually used at a dose of 1 mg before bedtime. Since there is no information regarding the use of TZ during breastfeeding, it may be preferred as an alternative drug when breastfeeding a newborn or premature baby. Side effects include dizziness and syncope (especially in the first dose), fatigue, headache, palpitations, impotence, incontinence, and gastrointestinal discomfort.[2,14,15] In one study, 165 patients who underwent transurethral ureteroscopic lithotripsy at a hospital were randomly divided into three groups and administered control, TZ, or combination therapy (terazosin and nifedipine).[16] Stone discharge rates and durations were also recorded, along with side effects and complications. The stone discharge rate of these patients in the combination group was significantly higher than in other groups, and the average discharge time was shorter in the combination group. Seventeen males (11 bladder neck obstruction (BNO) patients and 6 control volunteers) were included in another study.[17] A five-converter microtype catheter was used to measure pressure in the bladder, bladder neck, and membranous urethra during peeing, and 1 mg TZ was subsequently given to all subjects every day. TZ was found to be effective in opening the neck of the bladder and improving the hydraulic energy profile in males with BNO. Terazosin treatment does not affect prostate weight and histomorphology, and it induces caspase-3 expression as a potential molecular mechanism of apoptotic effect on prostate cells.[18] The chemical structure of TZ consists of piperazine and 2-furoyl and chloride, followed by catalytic hydrogenation and furan ring ends, and it is directly alkylated when heated in the presence of 2-chloro-6,7-dimethoxyquinazoline-4-amine.[19]

NEUROPROTECTION

Neuroprotective strategies are explored to protect the retina from degeneration in eye pathologies such as glaucoma, diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa.[20] In a coincidence seen as a result of these investigations, the retina appeared to prevent or delay neuroprotection and neuronal cell death. After the initial movement of the retina, it appears to maintain its neural function and thus has a defense mechanism designed to block vision loss. There is also the effect of neuroprotection to acute brain damage. Neuroprotective strategies that limit secondary tissue loss or improve functional outcomes are identified in multiple animal models of cerebral lesions with no ischemic, hemorrhagic, and traumatic effects. This potential intervention has been attempted to be used in randomized controlled trials in humans, but these studies have unfortunately yielded negative results.[21,22] Neuroprotection has been the center of attention because it stands out in the fight against diseases. Based on this popularity, some research has focused on determining whether several natural compounds, called nutraceuticals, can perform neuroprotective actions in the developing, adult, and aging nervous system.[13] A polyphenol called quercetin, commonly found in nature, has attracted the most attention in this regard. A study conducted in a laboratory environment have revealed evidence in animals and humans that quercetin is supportive of neuroprotective effects against neurotoxic chemicals or in various patterns of neuronal damage and neurodegenerative diseases. In a coducted study, when investigating the neuroprotective effect of oxygen, basically results related to stroke and TBH, and the oxygen paradigm revealed difference between experiments. Consequently, this study reviewed current comparative clinical trials of oxygen treatment among injuries in the nervous system.[23] The study aims to compare the efficacy and safety of normobaric oxygen and hyperbaric oxygen in the case of stroke and TBI. It could clarify the function of oxygen treatment in different nervous system injuries and give an overall view of oxygen in neuroprotection, which is thought to be a good indicator in clinical applications. To summarize, neurodegenerative diseases are among the most serious health problems affecting millions of people worldwide, and their incidence increases dramatically with increased life expectancy. These diseases often cause deficiencies in certain brain functions, and these are a heterogeneous group of chronic progressive disorders characterized by gradual neuron loss in the central nervous system. Alzheimer's disease (AD), PD, amyotrophic lateral sclerosis, multiple sclerosis, and Huntington's disease are the most common neurodegenerative

diseases. The etiology of most neurodegenerative diseases is mainly unknown, but it is widely accepted that they share the common molecules and cellular properties that contribute to the advances of these disorders.[24]

ALPHA BLOCKER

Alpha blockers prevent plain muscle contraction and inhibit smooth muscle by binding to alpha-1 adrenergic receptors. Benign prostatic hyperplasia and hypertension are among the major uses of alpha blockers. Terazosin is an example of an alpha-1 adrenergic receptor blocker. Venous capacitance increases in use for the treatment of hypertension, which then results in a drop in blood pressure. However, alpha blockers are not recommended for hypertension today, so they are not used as monotherapy. In the treatment of benign prostatic hyperplasia, alpha blockers are used to cause smooth muscle relaxation in the bladder, prostate, neck, and arterioles and are therefore used to treat urinary blockage symptoms. However, based on the detriment of alpha blockers, there has been an increase in heart failure, stroke, and cardiovascular disease.[25] A study attempted to evaluate the effects of alpha blockers, rather than the standard treatment, in adult people showing symptoms of urethral stone disease to examine the efficacy of medical expulsive therapy, which is commonly used to improve the stone passage of 1 cm or smaller ureter stones.[26] It was observed that alpha blockers increase stone clearance but slightly increase the risk of severe side effects, and it was concluded that they are less effective in 5 mm stones or stones smaller or larger than 5 mm stones.

TERAZOSIN AND BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia is a common disease that usually affects men. The prostate is an organ made up of walnut-sized smooth muscles at the lower base of the bladder in men. On the other hand, BPH is formed by the growth of the prostate as it ages. This disease is directly associated with LUTS and is becoming increasingly common in ageing men.[27,28] The diagnosis of BPH is performed by non-invasive ultrasound, followed by a grading process based on the shape of the prostate (intravesical prostatic protrusion) and height. The epimiography of contracting BPH in men is usually observed in those over 50 and 80 years of age and about 40% frequency. The symptoms are similar to various symptoms of LUTS, such as a complete sense of inactivity of the bladder and frequent urination.[29] Alpha blockers are considered the first option in the treatment of BPH-LUTS. However, 5-alpha reductase inhibitors (5-ARIs) are preferred in men with large symptomatic prostates.[30] Since TZ is a 5-ARI and an alpha blocker, it significantly improves LUTS and increases its peak, and drugs for mild to moderate BPH therapy have become a standard of care. Subsequently, after many clinical trials, the efficacy of two FDA-approved 5-ARIs (finasteride and dutasteride) and five alpha blockers (terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin) were confirmed.[31] 5-alpha reductase inhibitors and alpha-1 blockers are the main drugs used in the pharmacological treatment of BPH. In cases of severe BPH, it is recommended to use the pair combined. Terazosin is a selective alpha antagonist. Clinical trials have shown that TZ plays a role in the treatment of LUTS by helping the prostate and bladder to empty. Thus, it has been proven to be effective in the treatment of BPH symptoms.[32] A study investigated the effects of TZ and other drugs on rats with BPH and found that 0.5 mg of amlodipine significantly lowered the pressure of urinating in rats with BPH and increased the intermicturition duration.[33] When a combination of 0.5 mg amlodipine and 0.4 mg TZ was given, a great improvement was observed in rats with BPH. A similar rate of improvement was recorded in rats given 1 mg of TZ. Since BPH and LUTS patients are usually older, they may also have other clinical conditions. Therefore, the choice of treatment and medication is quite important. In this regard, TZ can be used safely as it also affects hypertension, which is highly prevalent in the elderly.[34]

TERAZOSIN AND PARKINSON'S DISEASE

Parkinson's disease, with close to six million people affected worldwide, is the second most common neurodegenerative disease. There has been a significant increase in PD cases over the past 30 years, and the rate of illness has increased as age progresses. Patients with

PD also have difficulty with motor symptoms, such as slow movements, tremors, along with neuropsychiatric abnormalities.[35,36] Terazosin studies in China have shown that it is activated by binding to the enzyme phosphoglycerate kinase 1 (PGK1), which is involved in the making of adenosine triphosphate (ATP), and the activation of PGK1 increases the ATP levels. The TZ's 2,4-diamino-6,7 methoxyisoquinazoline structure binds to PGK1 during adenosine diphosphate (ADP)-ATP binding. In this case, TZ increases PGK1, the ATP level rises, and apoptosis is inhibited. The increase in PGK1 by TZ in PD brought to mind whether there could be a condition slowing or preventing apoptotic neurodegeneration. Studies have been conducted in mice, rats, flies, and induced human stem cells to find the answer to this question.[37] It was observed that TZ reduces neurodegeneration caused by 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in mice. Adenosine triphosphate levels are reduced in human, monkey, and mouse models by MPTP, enabling PD formation with dopaminergic neuron loss. Terazosin's prevention of ATP decline allowed PD formation to slow as well.[37,38] Oxidopamine or 6-hydroxydopamine (6-OHDA), known for attention deficit and hyperactivity disorder, consumes immune activity in the middle brain in mice and rats, causing neurological diseases such as PD. Studies aimed to measure the effect of TZ after the induction of PD symptoms by injecting 6-OHDA into rats, and it was found that PGK1 activity along with TZ slowed neurodegeneration in rats.[37,39] Rotenone is a natural compound that consists of the roots of some tropical plants, and it causes symptoms of PD in rats and flies. Phosphoglycerate kinase 1 increase was observed by alleviating rotenone-induced neurodegeneration when the flies were given rotenone and then treated with TZ.[37,40] All of these studies support the idea that TZ can slow down PD.[37] Most neurodegenerative diseases occur as a result of the overwhelming activation of cell death. Since it is known to prolong apoptosis in studies on TZ, similar experiments have been carried out in sepsis-modeled organisms, and it has been observed that organ damage is minimized because it inhibits apoptosis. It is understood that TZ confers stress resistance by activating PGK1 and heat shock protein 90(HSP90). Terazosin interacts with PGK1 and causes an increase in ATP. As observed in studies, PGK1 regulates ATP increase by interacting with HSP90 ATPase.[10]

In conclusion, TZ, which is an alpha-1 antagonist, is used for the treatment of hypertension and BPH. Especially for BPH, it is the first choice in drug treatment. There was a considerable reduction in the number of patients undergoing surgery after TZ was administered as a medication in BPH patients. As a result of recent studies, the effectiveness of TZ on neurodegenerative diseases has also been proven. Especially in experiments on PD, it has been proven to reduce PD symptoms by inhibiting apoptosis. It is thought that TZ may also be effective on AD, a disease of the same scope as PD in terms of tissue damage size and formation. Terazosin interacts with the causative mechanism of many diseases, providing hope and welfare to patients.

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