Alpha-blockers for the Treatment of Benign Prostatic Hyperplasia

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KEYWORDS

• Alpha-blockers • BPH • Lower urinary tract symptoms • Medical management BPH

KEY POINTS

- Over the last 2 decades the evolution of alpha-blockers for lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) has been to preserve effectiveness, improve tolerability, and eliminate dose titration.
- Today, alpha-blockers represent the first-line treatment of most men with BPH whereby the primary objective is relief from bothersome LUTS.
- The thought that alpha blockers only improve LUTS by relieving BOO is likely an oversimplification.

The first selective alpha-blocker was approved for the treatment of lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) in 1992. The evolution of alpha-blockers for LUTS/BPH has been to preserve effectiveness and improve tolerability following administration of a single daily dose without requirement for dose titration. Today, alpha-blockers represent the first-line treatment of most men with BPH whereby the primary objective is relief from bothersome LUTS. The proposed mechanism of action, which is to decrease bladder outlet obstruction (BOO) via smooth muscle relaxation, is an oversimplification.

HISTORICAL PERSPECTIVE

The evolution of alpha-blockers for the treatment of BPH represents one of the first triumphs of translational medicine.

In 1975, Caine and colleagues[1] investigated the in vitro smooth muscle contractile properties of tissue strips derived from human prostates. Human prostate tissue was shown to elicit a strong contractile response in the presence of phenylephrine, a potent alpha agonist. At the time, the adrenergic receptors were subclassified simply as alpha and beta. The phenylephrine-induced contraction was inhibited by phenoxybenzamine, a selective inhibitor of alpha adrenoceptors. Based on these experiments, Caine and associates[1] proposed that the pathophysiology of BPH was mediated in part by prostate smooth muscle tension and speculated that the disease would be effectively treated by alpha-blockade.

In 1975 Caine and colleagues[2] published the first study suggesting alpha-blockers were effective for the treatment of BPH. A subsequent randomized placebo-controlled study confirmed that phenoxybenzamine improved both uroflow rates and prostatism, which at the time was the terminology describing LUTS arising from the enlarged prostate.[3] The primary limitation of phenoxybenzamine was the adverse events, including high rates of tiredness, dizziness, impaired ejaculation, nasal stuffiness, and hypotension. The use of phenoxybenzamine never gained widespread use for treating BPH.

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DEVELOPMENT OF SELECTIVE ALPHA1 BLOCKERS FOR BENIGN PROSTATIC HYPERPLASIA

In the early 1980s, the alpha adrenoceptors were subclassified into alpha 1 and alpha 2. Lepor and Shapiro[4] were first to characterize both the alpha 1 and alpha 2[5] adrenoceptors in human prostate tissue using radio-ligand binding studies and subsequently observed that the contractile properties of prostate smooth muscle was mediated primarily by the alpha 1 subtype.[6]

Prazosin was one of the first alpha 1 blockers developed for the treatment of hypertension. The first multicenter randomized placebo-controlled trial of any selective alpha 1 blocker for symptomatic BPH was reported my Kirby and colleagues.[7] Prazosin significantly improved both the severity of prostatism and peak flow rate (PFR) compared with placebo.

The primary advantage of prazosin over phenoxybenzamine was better tolerance presumably by eliminating the adverse events mediated by alpha 2 adrenoceptor blockade. Although a legitimate comparative trial between prazosin and phenoxybenzamine was never performed, the effectiveness of the two drugs seems to be comparable. Like phenoxybenzamine, the limitation of prazosin was the first dose effect, which required a dose titration to an effective multiple daily dose. No effort was made to seek Food and Drug Administration (FDA) approval for prazosin for the indication of symptomatic BPH presumably because of the limited patent life and the lack of general interest in developing and bringing to market medical therapy for BPH.

The next major advance in the development of alpha-blockers for the treatment of symptomatic BPH was the availability of long-acting selective alpha 1 blockers, such as terazosin and doxazosin. Both drugs were approved by the FDA for the treatment of hypertension in the 1980s. The longer half-life of both drugs allowed for once-daily dosing.

Terazosin was the first of the long-acting selective alpha 1 blockers to be approved by the FDA for the treatment of symptomatic BPH in 1992. Three randomized multicenter placebo-controlled studies leading to the approval of terazosin showed significant treatment-related decreases in symptom severity and increases in PFR over placebo[8–10] (**Fig. 1**). The author served as the national principal investigator for the first randomized study comparing placebo, 2, 5, and 10 mg of terazosin.[8] Because of the potential safety concerns associated with administering an antihypertensive drug to normotensive men, all subjects were admitted to a monitored hospital facility for 72 hours. The requirement for 3-day hospital observation greatly limited patient accrual. Eventually, the FDA relaxed the in-hospital monitoring requirement to 24 hours and the study was completed. The titration to fixed-dose study was not powered to show whether differences between the doses were statistically significant, although there was a suggestion that improvement in LUTS was dose dependent. Overall, terazosin was well tolerated. Asthenia/fatigue, postural hypotension, dizziness, and somnolence were the treatment-related adverse events (**Table 1**).

The FDA required a long-term extension study in order to demonstrate the durability of efficacy.

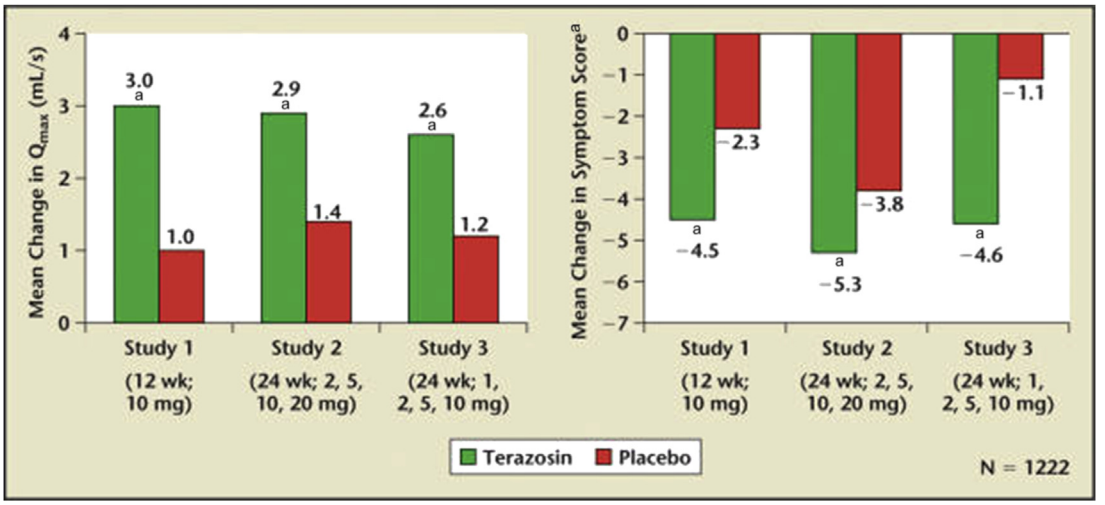

Fig. 1. The effect of terazosin on LUTS and PFR relative to placebo. Q_{max}, maximum urinary flow. [a] $P \leq .05$ versus placebo. (*From* Lepor H. The evolution of alpha-blockers for the treatment of benign prostatic hyperplasia. Rev Urol 2006:8(Suppl 4):53–9; with permission.)