Personalized therapeutics of $\alpha_1$-blockers in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

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Dear editor

We read with great interest the multicenter, prospective, comparative cohort study by Zhang et al¹ who suggested that patients with uncontrolled or untreated hypertension and lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS) should be warned about a decrease in blood pressure on initiation of alfuzosin 10 mg therapy alone or concomitantly with antihypertensive medication. Here we discuss and share our perspectives on this issue.

$\alpha_1$-blockers are the most frequently prescribed medical therapy in the treatment of BPH/LUTS. A number of $\alpha_1$-blockers (alfuzosin, doxazosin, terazosin, tamsulosin, naftopidil, silodosin) have been approved for the treatment of BPH throughout the world; however, they exhibit different selectivity toward $\alpha_1$-adrenoceptor (AR) subtypes. Three types of $\alpha_1$-AR subtypes ($\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$) are found in human tissue. The $\alpha_{1A}$ subtype is located in the human prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra, and mediates contraction of the smooth muscle in these tissues. In addition to $\alpha_{1A}$-ARs, $\alpha_{1B}$-ARs are also present to a significant extent in the human prostate, and $\alpha_{1D}$-ARs are thought to mediate contraction of human arteries.²

The early $\alpha_1$-blockers (alfuzosin, doxazosin, terazosin) were nonselective for subtype and were associated with blood pressure-related adverse effects, such as orthostatic hypotension.³ Sato et al compared the binding affinity of tamsulosin for human $\alpha_1$-AR subtypes with that of other $\alpha_1$-blockers, ie, silodosin, terazosin, alfuzosin, and naftopidil.⁴ Tamsulosin has relative selectivity for the $\alpha_{1A}$-subtype and $\alpha_{1D}$-subtype ($\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$), and naftopidil has relative selectivity for the $\alpha_{1B}$-subtype ($\alpha_{1D} \geq \alpha_{1A} > \alpha_{1B}$). The affinity of tamsulosin for the human $\alpha_{1A}$-AR was, respectively, 5-fold, 120-fold, 280-fold, and 400-fold higher than that of silodosin, terazosin, alfuzosin, and naftopidil, respectively. However, the $\alpha_{1B}$-AR binding affinity of silodosin was shown to be much lower than that of tamsulosin in vitro.⁵ The selectivity of silodosin towards the $\alpha_{1A}$-AR subtype versus the $\alpha_{1B}$-AR subtype ($\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$) was reported to be 38-fold higher than that of tamsulosin in studies using transgenic Chinese hamster ovary cells.⁶,⁷ The selectivity ratio ($\alpha_{1A}/\alpha_{1D}$) for terazosin, doxazosin, alfuzosin, tamsulosin, and silodosin was 0.3, 0.4, 0.5, 6.3, and 166, respectively.⁸ The unique AR selectivity profile of silodosin minimizes the propensity for blood pressure-related adverse effects caused by $\alpha_1$-AR blockade.⁹ Regarding the efficacy of subtype-selective $\alpha_1$-blockers in the management of BPH, expression of $\alpha_1$-AR subtype mRNA was observed as a predictor. Tamsulosin hydrochloride was more effective in patients with dominant
expression of the \( \alpha_{1a} \)-AR subtype, whereas naftopidil was more effective in those with dominant expression of the \( \alpha_{1d} \)-AR subtype.\(^\text{10}\)

With respect to the indications for \( \alpha_{1} \)-blockers, doxazosin and terazosin are currently indicated for the treatment of both hypertension and BPH/LUTS, and are more likely to impair safety-relevant physiological blood pressure control in normotensives with LUTS than are tamsulosin and silodosin.\(^\text{11,12}\)

Alfuzosin is only indicated for treatment of BPH/LUTS. The study by Zhang et al demonstrated that alfuzosin 10 mg has no clinically important effects on blood pressure when used to treat BPH/LUTS in men who were physiologically normotensive or had hypertension controlled by antihypertensive medication. The relevance of their finding is that it provides reassurance for clinicians when prescribing alfuzosin 10 mg for a patient who is already on antihypertensive therapy, without the need to worry about the risk of hypotensive episodes. However, alfuzosin 10 mg significantly decreased blood pressure in patients with uncontrolled or untreated hypertension, indicating that such patients require careful evaluation before initiating alfuzosin therapy.\(^\text{1}\) The study by Zhang et al further indicates that the clinical selectivity and cardiovascular safety of \( \alpha_{1} \)-blockers are related to patient-treatment interactions (comedication and comorbidity), and their finding will enrich our knowledge about the personalized therapeutics of \( \alpha_{1} \)-blockers in the treatment of BPH/LUTS.\(^\text{1}\) However, the vasodilatory adverse events of alfuzosin are related to dose, dosage interval, and formulation, i.e., they are less frequent with once-daily, sustained-release alfuzosin 10 mg than with the three times daily 2.5 mg formulation (6.3% versus 9.4%, respectively).\(^\text{13}\) Therefore, clinicians should be cautious about extrapolating the finding of the study by Zhang et al to treatment of BPH/LUTS with an immediate-release formulation of alfuzosin.\(^\text{1}\)

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**Disclosure**

The authors report no conflicts of interest in this work.

**References**


4. Sato S, Hatanaka T, Yuyama H, et al. Tamsulosin potently and selectively antagonizes human recombinant \( \alpha(1A/1D) \)-adrenoceptors: slow dissociation from the \( \alpha(1A) \)-adrenoceptor may account for selectivity for \( \alpha(1A) \)-adrenoceptor over \( \alpha(1B) \)-adrenoceptor subtype. *Biol Pharm Bull*. 2012;35:72–77.


Deaths in the study were reported by the treating physicians to the study coordinators, who reviewed the data. The follow-up period was 36 months. The study was designed to assess the long-term safety and efficacy of the new formulation of alfuzosin.

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References


