Add-on therapy with doxazosin in patients with hypertension influences arterial stiffness and albuterol-mediated arterial vasodilation

Andrzej Wykretowicz, Przemysław Guzik, Tomasz Krauze, Karolina Adamska, Agata Milewska & Henryk Wysocki

Division of Cardiology-Intensive Therapy, Poznan University of Medical Sciences, Poznan, Poland

What is already known about this subject

- Hypertension is associated with increased arterial stiffness and impaired endothelial function.
- Arterial vasodilation depends on endothelial function and can be regulated by β_2 -adrenergic stimulation.
- Doxazosin is a known and potent antihypertensive agent. However, its effects on arterial stiffness and vasodilation have not been fully established.

What this study adds

Sixteen-week add-on antihypertensive therapy with 4 mg of doxazosin extended release daily:

- Reduces arterial stiffness.
- Improves albuterol-mediated, i.e. endothelium-dependent, arterial vasodilation.
- Does not influence nitroglycerin-mediated, i.e. endothelium-independent, arterial vasodilation.

Correspondence

Andrzej Wykretowicz, MD, Division of Cardiology-Intensive Therapy, Poznan University School of Medical Sciences, 49 Przybyszewskiego, 60–355, Poznan, Poland.
Tel. +48 6 1869 1391
Fax: +48 6 1869 1689
E-mail: awykreto@ptkardio.pl

Keywords

ACE inhibitors, arterial stiffness, doxazosin, endothelial dysfunction

Received

1 February 2007

Accepted

14 May 2007

Published OnlineEarly

17 July 2007

Aims

Doxazosin is an antihypertensive agent with largely unknown effects on arterial stiffness and vasodilation. The aim of this study was to determine the effect of the addition of doxazosin extended-release (ER) to the standard management of hypertension in patients with inadequately controlled blood pressure (BP) on arterial stiffness and arterial vasodilation.

Methods

Twenty patients with inadequately controlled hypertension were treated with 4 mg doxazosin ER daily for 16 weeks as an adjunct to their existing antihypertensive regimen.

Results

Doxazosin ER add-on therapy was associated with significantly reduced systolic ($P < 0.0001$) and diastolic ($P = 0.0003$) BP, improved arterial stiffness (determined by digital volume pulse analysis ($P = 0.048$)) and albuterol-mediated arterial vasodilation ($P = 0.030$).

Conclusions

Add-on therapy with 4 mg of doxazosin ER daily reduces BP and arterial stiffness and improves arterial vasodilation in response to adrenergic stimulation.

Introduction

Increased arterial stiffening and endothelial dysfunction are risk factors for the development of, or may result from, hypertension [1]. Various mechanisms are involved in this mutual relationship with reactive oxygen species generated by different cells circulating in the blood or present in the arterial walls [2]. Reactive oxygen species can interact with a number of substances, including lipids transported in lipoproteins, and thus promote the development of atherosclerosis.

Increased stiffening of the arterial wall results in changes in the peripheral pulse contour, as measured by the digital volume pulse (DVP) [3]. Analysis of the timing of discrete components of the DVP helps to define the stiffness index (SI_{DVP}), which is related to large artery stiffness. In addition, the reflection index (RI_{DVP}), formulated from the DVP analysis, represents a measure of the amount of pulse wave reflection and the tone of small arteries. The response of the RI_{DVP} to an endothelium-dependent vasodilator, e.g. salbutamol, a β_2 -adrenergic agent, provides a useful non-invasive measure of endothelial cell function [4, 5].

Doxazosin's positive effects on dyslipidaemias, as well as its antiatherosclerotic and free radical scavenging properties, suggest that it is useful in a combined treatment of hypertension [6, 7]. Considering the favourable effects of doxazosin on vascular wall properties, we sought to determine whether the addition of doxazosin extended-release (ER) to the standard management of hypertension in patients with inadequately controlled blood pressure (BP) who were already receiving at least two antihypertensive agents would affect: (i) arterial stiffness and (ii) albuterol-mediated arterial vasodilation.

Materials and methods

Twenty patients with inadequately controlled mild-to-moderate essential hypertension (average BP $\geq 140/90$ mmHg despite treatment consisting of at least two drugs) were recruited after giving their informed consent. The use of long-acting nitrates and the introduction of statins during the study were not allowed. The institutional ethics committee approved the study protocol.

This was an open, proof-of-concept study lasting 16 weeks. Doxazosin 4 mg was given once a day in an ER form (Cardura XL; Pfizer, Groton, CT, USA) as an adjunct to their on-going antihypertensive treatment. BP was measured in a sitting position after 10 min rest, with an oscillometric method (Omron M-5; Omron Healthcare, Milton Keynes, UK) on the patient's arm, and revealed higher BP during the first visit. The BP mea-

surements were obtained from each patient, using the same sphygmomanometer, before morning antihypertensive medications, both at baseline and at the end of the study.

Assessment of arterial stiffness was performed using a photoplethysmograph (Pulse Trace 2000; Micro-Medical, Rochester, UK) [3]. To assess endothelium-independent arterial vasodilation, 50 μ g of nitroglycerin (NTG) (Perlinganit; Schwarz Pharma AG, Monheim, Germany) was administered sublingually. To assess endothelium-dependent arterial vasodilation, 2×200 μ g of albuterol (Salbutamol; GlaxoSmithKline Pharmaceuticals, Brentford, UK) was given by inhalation during 60 s of slow breathing through a spacer. The arterial vasodilation, independent of or dependent on endothelial function, was defined as the maximum difference in ΔRI_{DVP} between baseline and the post-NTG or postalbuterol period, respectively [4, 5].

Continuous data are shown as mean $\pm$ standard error of the mean (SEM). Due to the nonparametric distribution of the data, comparisons between groups were made using the Wilcoxon test for paired data. Statistical significance was set at $P < 0.05$ and the statistical analyses were performed using Prism 4.03 for Windows (Graph-Pad Software, San Diego, CA, USA).

Results

The studied patients were middle aged (57 ± 4 years old), slightly obese (body mass index 30.5 ± 4 kg m $^{-2}$) and with a moderate increase in total cholesterol, low-density lipoprotein (LDL) and triglyceride levels (210 ± 39 mg dl $^{-1}$, 127 ± 37 mg dl $^{-1}$ and 163 ± 98 mg dl $^{-1}$, respectively). The concentrations of high-density lipoprotein (HDL) (52 ± 19 mg dl $^{-1}$), creatinine (0.9 ± 0.2 mg dl $^{-1}$) and fasting glucose (93 ± 11 mg dl $^{-1}$) were normal. There were nine women, one a survivor of myocardial infarction, and 10 patients with stable angina pectoris. Two of the group had diabetes and seven were active smokers. All patients were receiving antihypertensive therapy with either an angiotensin converting enzyme inhibitor ($n = 18$) or an angiotensin-2 receptor blocker ($n = 2$). Eleven subjects being treated with a β -adrenergic blocker, eight with a calcium-channel blocker, 13 with a diuretic and six with statin.

When compared with the baseline BP readings, there were significant reductions in systolic, diastolic and mean BP at the study end (Table 1). By comparison with the baseline DVP, there was a significant reduction in SI_{DVP} and an increase in postalbuterol ΔRI_{DVP} following treatment with 4 mg of doxazosin ER (Figure 1). The NTG-induced arterial vasodilation was not changed by this form of treatment.

Table 1

Blood pressure and other haemodynamic variables at baseline and at the study end after 16 weeks of add-on therapy with 4 mg of doxazosin extended release

Measurements	At baseline	At study end After all morning drugs	<i>P</i>	Without morning drugs	<i>P</i>
SBP (mmHg)	158 ± 3	130 ± 2	<0.0001	139 ± 4	0.0002
DBP (mmHg)	91 ± 2	81 ± 2	0.0003	81 ± 3	<0.0001
MBP (mmHg)	113 ± 2	97 ± 2	<0.0001	100 ± 3	<0.0001
HR (bpm)	64 ± 3	63 ± 3	NS	62 ± 2	NS

Results are shown as mean ± SEM. SBP, Systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; bpm, beats per minute.

Figure 1

Comparison of arterial stiffness and post-NTG or postalbuterol arterial vasodilation at baseline and at the study end after 16 weeks of add-on therapy with 4 mg of doxazosin extended release. (A) The values of SI_{DVP} representing arterial stiffness. (B) The values of changes in RI caused by NTG or albuterol. SI_{DVP} , Stiffness index by digital volume pulse analysis; ΔRI_{DVP} , the change in reflection index by digital volume pulse analysis; NTG, nitroglycerin; NS, not significant.

Discussion

In this study, we found that the addition of 4 mg of doxazosin ER per day for 16 weeks to the treatment of inadequately controlled hypertension improved arterial BP control and had beneficial effects on arterial stiffness (SI_{DVP}) and β_2 -adrenergic arterial vasodilation. The NTG-mediated arterial vasodilation was not affected by this treatment.

It is not clear whether the improvement in SI_{DVP} and albuterol-mediated ΔRI_{DVP} is secondary to the mechanical effects of BP reduction, to interactions with the autonomic nervous system, a direct influence of doxazosin on the arterial walls and endothelial cells or the combined effect of these mechanisms. The use of multidrug

antihypertensive treatment further complicates the matter, since the various medications affect arterial stiffness and endothelial function differently [8]. Nevertheless, the addition of 4 mg of doxazosin ER to the treatment of uncontrolled hypertension has some beneficial effects on the functional properties of arterial walls.

The fact that the changes in BP did not correlate with either SI_{DVP} or ΔRI_{DVP} (data not shown) suggests that some additional mechanisms of doxazosin action might be responsible for the findings. Doxazosin interacts with the sympathetic nervous system [9, 10]. Its short-acting form causes a sympathetic stimulation, increasing the amount of circulating catecholamines and heart rate acceleration. By contrast, doxazosin ER

reduces the heart rate, which suggests a beneficial influence on the sympathetic tone [11]. The baseline heart rate was not changed at the study end, which implies a neutral effect of doxazosin ER on sympathetic activity.

Doxazosin increases the concentration of HDL and reduces the concentrations of LDL-cholesterol and uric acid [6, 7]. Some doxazosin metabolites, namely 6- and 7-hydroxydoxazosin, have radical scavenging properties [12]. These additional features of the drug may contribute to the mechanisms responsible for our findings.

Some important limitations of our study are the lack of placebo control, of head-to-head comparison with other antihypertensives, and of double-blinding to the add-on treatment. Nevertheless, our add-on treatment with doxazosin ER to a regimen of drugs potentially affecting arterial wall function was associated with an improvement in arterial stiffness and endothelium-dependent vasodilation.

This study was supported by an unrestricted International Competitive Cardura Award research grant from Pfizer Inc. The authors are indebted to Professor Geoffrey Shaw for his editorial assistance.

References

- 1 Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension* 2005; 46: 1118–22.
- 2 Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? *Hypertension* 2004; 44: 248–52.
- 3 Millasseau SC, Kelly RP, Ritter JM, Chowienczyk PJ. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Clin Sci (Lond)* 2002; 103: 371–7.
- 4 Chowienczyk PJ, Kelly RP, MacCallum H, Millasseau SC, Andersson TLG, Gosling RG, Ritter JM, Anggard EE. Photoplethysmographic assessment of pulse wave reflection: blunted response to endothelium-dependent beta2-adrenergic vasodilation in type II diabetes mellitus. *J Am Coll Cardiol* 1999; 34: 2007–14.
- 5 Wilkinson IB, Hall IR, MacCallum H, Mackenzie IS, McEniery CM, van der Arend BJ, Shu YE, MacKay LS, Webb DJ, Cockcroft JR. Pulse-wave analysis clinical evaluation of a noninvasive, widely applicable method for assessing endothelial function. *Arterioscler Thromb Vasc Biol* 2002; 22: 147–52.
- 6 Black HR. Doxazosin as combination therapy for patients with stage 1 and stage 2 hypertension. *J Cardiovasc Pharmacol* 2003; 41: 866–9.
- 7 Campo C, Segura J, Roldan C, Alcazar JM, Rodicio JL, Ruilope LM. Doxazosin GITS versus hydrochlorothiazide as add-on therapy in patients with uncontrolled hypertension. *Blood Press Suppl* 2003; 2: 16–21.
- 8 Van Bortel HL, Struijker-Boudier AJ, Safar ME. Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension* 2001; 38: 914–21.
- 9 Furberg CD. Doxazosin, an inferior antihypertensive agent? *J Hum Hypertens* 2002; 16: 375–7.
- 10 Takata Y, Yoshizumi T, Ito Y, Hirota Y, Fujishima M. Effect of administration and withdrawal of doxazosin on ambulatory blood pressure in patients with essential hypertension. *Angiology* 1995; 46: 11–8.
- 11 de Alvaro F, Hernandez-Presa MA; ASOCIA Study. Effect of doxazosin gastrointestinal therapeutic system on patients with uncontrolled hypertension: the ASOCIA Study. *J Cardiovasc Pharmacol* 2006; 47: 271–6.
- 12 Brude IR, Drevon CA, Viken K, Amstad JE, Valnes KN, Nenseter MS. Doxazosin treatment and peroxidation of low-density lipoprotein among male hypertensive subjects: *in vitro* and *ex vivo* studies. *Biochem Pharmacol* 1999; 58: 183–91.