Doxazosin

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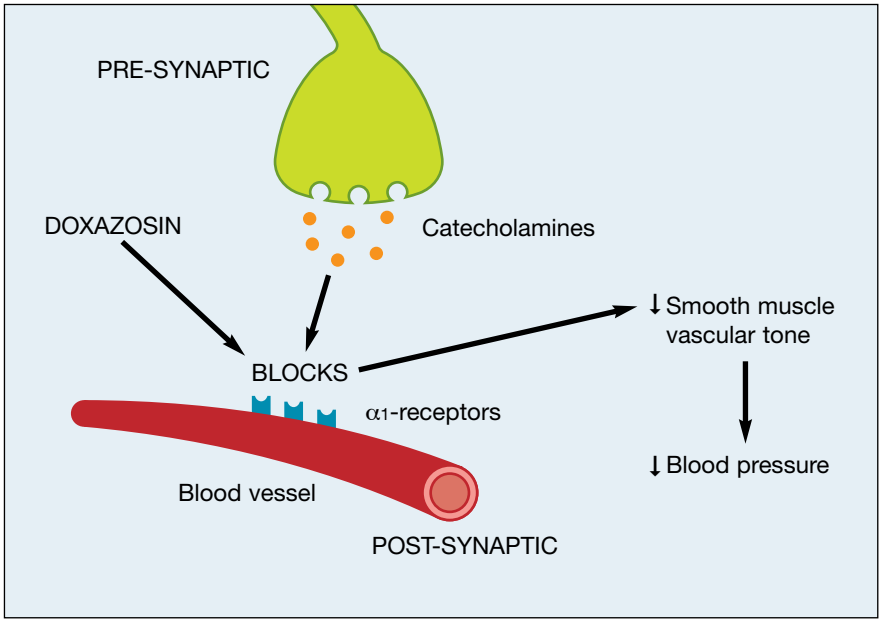
Introduction

At the end of the 19th century, Oliver and Schafer found that injecting dogs with a substance derived from the adrenal glands of sheep caused a rise in arterial pressure. In 1913, the pharmacologist Dale observed that adrenaline constricted some blood vessels while relaxing others and, in 1948, Ahlquist postulated the existence of α- and β-adrenoceptors based on the rank order of potency of various catecholamines. In 1964, the β-adrenoceptor antagonist propranolol was launched and revolutionised the management of ischaemic heart disease. In 1976, Pfizer was given approval to market the α-adrenoceptor antagonist prazosin as an antihypertensive drug; this was followed in the early 1980s by doxazosin which, in 1995, was licensed for use in benign prostatic hypertrophy (BPH). In 2002, a sustained release preparation of doxazosin was added to the formulary coinciding with the withdrawal of the most widely prescribed dose of non-sustained release doxazosin.

Pharmacology

Figure 1 outlines the pharmacological action of doxazosin. It is a synthetic quinazoline compound which competitively inhibits the post-synaptic α1-adrenoceptor in the autonomic nervous system. Blocking the interaction of endogenous catecholamines and the α1-adrenoceptor results in reduced vascular smooth muscle tone, vasodilatation, reduced total peripheral resistance and hence a hypotensive effect. This hypotensive effect is opposed by baroreceptor reflexes causing, at least in the short term, an increase in heart rate. The potential for postural hypotension is offset by a degree of salt and water retention.

Figure 1. Pharmacological action of doxazosin at sympathetic nerve synapse



In general, doxazosin is well tolerated; the main reported side effects relate to its antihypertensive effect and, in particular, first dose hypotension and postural hypotension. Headache, nausea, fatigue and a degree of peripheral oedema are less frequently reported. Doxazosin is largely (98%) protein-bound, but has no significant effect on the protein binding of other drugs such as digoxin or warfarin. Doxazosin can be used safely with all other classes of antihypertensive agent, its only significant drug interaction being to potentiate the antihypertensive effect. Though there are no reports of teratogenicity, the manufacturer advises avoidance in pregnancy and, as it is known to accumulate in breast milk, it should also be avoided in breast-feeding mothers.

In addition to the effects on blood pressure, antagonism of the α1-adrenoceptors in prostatic stromal and bladder neck tissue reduces the tone of smooth muscle at these sites thus relieving the urinary outflow obstruction symptoms experienced by those suffering from BPH. Furthermore, long-term effects of doxazosin, possibly independent of its α-blocking actions, may include apoptosis of prostatic cells and, therefore, ameliorate the progression of BPH.

Finally, doxazosin is known to have a number of metabolic effects the clinical significance of which is uncertain. Doxazosin has been demonstrated to favourably alter atherogenic lipid profile (reduced triglycerides and LDL, increased HDL), and improve insulin sensitivity.

Trials of safety and efficacy

The Hypertension and Lipid Trial (HALT) recruited 851 patients to an open, non-comparative multi-centre

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trial of doxazosin in individuals with essential hypertension (sitting diastolic blood pressure 96–110mmHg).[1] Patients were either on no prior medication, or were taken off their current antihypertensive drug (in which case a one-week 'washout' period was required). After a maximum study period of 16 weeks, both sitting and standing blood pressure were significantly reduced (15.2/12.5mmHg and 16.1/12.7mmHg respectively) with no significant change in heart rate. Furthermore, there were small but significant reductions in triglyceride levels, total and LDL-cholesterol (2.7%, 2.4% and 3.4% respectively), but no effect on HDL-cholesterol. In this manufacturer-sponsored study, doxazosin was promoted as an effective antihypertensive drug which, because of its additional effects on lipid profile, may offer additional reduction of the risk of subsequent cardiovascular events.

Enthusiasm for the use of doxazosin as an antihypertensive agent began to wane with the publication of an interim report from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[2] This randomised, double-blind, active-controlled clinical trial recruited over 42 000 individuals aged ≥55 years with hypertension and at least one additional cardiovascular risk factor. Four different antihypertensive regimens were compared: chlorthalidone (a thiazide diuretic), doxazosin, amlodipine (a dihydropyridine calcium channel antagonist) and the ACE inhibitor lisinopril. A total of 24 335 patients received either doxazosin or chlorthalidone, among whom those on chlorthalidone had a significantly lower risk of combined cardiovascular disease events (coronary heart disease death, non-fatal myocardial infarction, stroke, angina, coronary revascularisation, congestive heart failure, and peripheral arterial disease). More strikingly, when these endpoints were considered separately, patients treated with doxazosin had double the risk of being hospitalised with congestive heart failure. The doxazosin arm of the trial was therefore discontinued early.

Sympathetic regulation of smooth muscle tone via α_1-adrenoceptors in the bladder neck and prostate plays a major role in the urinary obstructive symptoms suffered by patients with BPH. Doxazosin was shown in placebo-controlled, double-blind trials, in both normotensive and hypertensive men, to improve urinary flow rates and obstructive symptoms. Subsequently, the Medical Therapy of Prostatic Symptoms (MTOPS) trial has demonstrated that in the long term doxazosin, in combination with the 5α-reductase inhibitor finasteride, slows progression of BPH and reduces the risk of urinary retention and need for surgical treatment.[3]

Specific evidence for use in diabetes

Notwithstanding the observation that doxazosin marginally improves lipid profile in patients without diabetes and insulin sensitivity in those with disorders of glucose metabolism, there is no evidence that doxazosin is especially beneficial in patients with diabetes. Furthermore, a subgroup analysis of patients with diabetes or impaired glucose tolerance in the ALLHAT study revealed the same increase in risk of combined cardiovascular disease or congestive heart failure following treatment with doxazosin rather than chlorthalidone as in those with normal glucose metabolism.[4]

Discussion

The current British Hypertension Society guidelines advocate ACE inhibitors in those under 55, and calcium channel antagonists or thiazide diuretics in older or black patients as first-line treatment of hypertensive individuals. A series of steps are then advised until target blood pressure is achieved. Only after a patient is on the combination of ACE inhibitor, calcium channel antagonist and a thiazide diuretic, should an α-blocker be considered, and even then it is only one of a number of options including use of a β-blocker or addition of a further diuretic.

In summary, therefore, doxazosin is an efficacious antihypertensive drug with additional benefits for patients suffering from BPH. Following the ALLHAT study, significant safety concerns regarding the increased risk of combined cardiovascular endpoints, including the risk of developing congestive heart failure, persist. The most recent guidelines for the treatment of hypertension in both the UK and the US recommend the use of doxazosin or other α-blockers, in the absence of a compelling indication such as BPH, only as a fourth or fifth line measure.

Key points

- Doxazosin is an α-blocker, and is a treatment for hypertension and benign prostatic hypertrophy
- In a major trial, doxazosin was less effective than a diuretic, calcium-channel blocker and ACE inhibitor in reducing cardiovascular events
- Hypertension guidelines therefore recommend the use of doxazosin if other drugs fail to control blood pressure or are contraindicated

Conflict of interest statement

Dr Mackinnon and Dr McKay have no conflicts of interest to declare. Dr Fisher has received lecture fees from and has served on advisory boards for Pfizer.

References

1. Levy D, Walmsley P, Levenstein M. Principal results of the Hypertension and Lipid Trial (HALT): a multicenter study of doxazosin in patients with hypertension. *Am Heart J* 1996; **131:** 966–973.
2. Major cardiovascular events in hypertensive patients randomized to doxazosin *vs* chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000; **283:** 1967–1975.
3. McConnell JD, Roehrborn CG, Bautista OM, *et al.* The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; **349:** 2387–2398.
4. Barzilay JI, Davis BR, Bettencourt J, *et al.* Cardiovascular outcomes using doxazosin *vs.* chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. *J Clin Hypertens (Greenwich)* 2004; **6:** 116–125.