Commentary

Benefits and side effects of blood pressure lowering treatment: what was wrong with doxazosin in the ALLHAT?

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Abstract

The lowering of high blood pressure is supposed to protect target organs from hypertensive damage. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial was designed to compare the cardioprotective properties of three antihypertensives from different classes (lisinopril, amlodipine and doxazosin) with chlorthalidone. Despite effective blood pressure lowering and a favorable metabolic profile, the doxazosin arm of the trial had a significantly higher relative risk of cardiovascular disease and heart failure compared with the chlorthalidone arm. This article speculates on possible causes for this unexpected result and suggests that the culprit may be accentuation of the vascular effects of vasopressin, which are maximized under α-adrenergic blockade. These findings may have implications for the large number of older men who receive monotherapy with α-blockers for treatment of prostatic symptoms.

Keywords α_1-adrenoceptor blockade, coronary constriction, ischemic heart disease, vasopressin

The purpose of lowering high blood pressure is to prevent morbidity and mortality from hypertensive complications, such as heart attack, stroke, renal failure, and heart failure. The Veterans Administration studies in the 1960s proved beyond doubt that treating hypertension with thiazides and β-blockers (the drugs available at that time) significantly diminished the rates of strokes, renal failure, and heart failure, although the decrease in the rate of myocardial infarcts did not reach statistical significance. It has been estimated that a 10–15 mmHg fall in systolic blood pressure should lead to a 15% reduction in relative risk for heart attack and to a 40% reduction for stroke [1].

Effects of antihypertensive agents

With the advent of new classes of antihypertensive agents, the emphasis shifted from efficacy in lowering blood pressure, which is taken for granted, to potential to protect against end-organ damage. Controlled clinical trials have indicated that drugs from different classes have different neurohumoral and metabolic profiles, which might enhance or partially offset the benefits from blood pressure lowering *per se*. For example, thiazides and β-adrenergic blockers have been reported to further increase insulin resistance, and hence to accentuate the dysmetabolic syndrome that commonly accompanies essential hypertension [2,3]. On the contrary, α_1-adrenergic blockers and angiotensin-converting enzyme (ACE) inhibitors have been reported to improve insulin sensitivity and the lipid profile [4], whereas calcium-channel blockers were found to be metabolically neutral. In terms of neurohormonal changes, the stimulation of the renin–angiotensin and sympathetic systems associated with the use of diuretics and dihydropyridines should be detrimental to end organs, whereas angiotensin blockers and sympathetic blockers should be beneficial to them. Several such effects that are theoretically considered to be beneficial have been used as 'surrogate endpoints' in the absence of firm data on morbidity and mortality.

Improvement in surrogate endpoints may be encouraging but is not always predictive of real endpoints, and should

ACE = angiotensin-converting enzyme; AVP = arginine vasopressin.
ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial.

not be sufficient to influence clinical decisions. This was shown repeatedly by recent trials (e.g. with estrogen replacement or various antioxidants), where amelioration in various markers did not result in improved cardiovascular outcomes [5]. Nevertheless, clinical trials on selected subpopulations as well as meta-analyses of pooled data suggest that, at levels producing a similar blood pressure lowering effect, β-blockers were cardioprotective and ACE inhibitors were both cardioprotective and nephroprotective, while calcium-channel blockers might offer better protection from stroke [6].

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These newer classes have not strictly speaking been proven to reduce morbidity and mortality from hypertension, as they could not ethically be tested against placebo. They could, however, be tested against 'the gold standard', a thiazide that has been proven to reduce morbidity and mortality in the placebo-controlled trials. This is what led to the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [7]. The double-blind, active-controlled component of the ALLHAT was designed to determine whether the rate of the primary outcome (a composite of fatal myocardial infarcts and nonfatal coronary events) would be different in high-risk older patients treated with a drug from each one of three classes of antihypertensives, an ACE inhibitor (lisinopril), a calcium blocker (amlodipine), or an α_1-adrenergic blocker (doxazosin), compared with patients treated with a thiazide diuretic (chlorthalidone).

The trial started in February 1994 and, after an interim analysis in January 2000, an independent review committee recommended that the doxazosin arm be discontinued. This was because, compared with chlorthalidone, doxazosin had a significantly higher relative risk of stroke (1.19) and of combined cardiovascular disease (relative risk = 1.25), and a more than double risk of congestive heart failure (relative risk = 2.04) [8].

This unexpected outcome sparked a lot of discussion, dismay, and speculation. There was dismay that, once more, improvement in surrogate endpoints (blood pressure, lipid profile, and other parameters of the dysmetabolic syndrome) did not translate into favorable outcomes. There was speculation on what concurrent changes might have over-ridden the benefits of those improvements. We would like to add our own plausible, although speculative, explanation for these findings.

Explaining the doxazosin findings in the ALLHAT

In addition to the renin–angiotensin and the sympathoadrenal systems, arginine vasopressin (AVP) is the third major systemic pressor hormone [9]. Its pressor function is partly offset by its sensitizing influence on baroreflexes [10,11], not fully apparent until the other two systems have been impaired [12]. The importance of AVP to systemic or regional vascular resistance cannot necessarily be predicted from the circulating levels, as it is markedly increased after effective sympathetic inhibition even in the absence of a further increase in plasma levels. It can only be accurately estimated from the response to a selective antagonist of the V_1 type receptors of AVP. Using such a pharmacologic probe, we have found that the pressor action of AVP is maximized after α_1-adrenergic blockade [13]. Under certain conditions, AVP becomes an important vasopressor factor in patients with hypertension [12] and/or congestive heart failure [14]. Its pressor influence is most apparent in patients with autonomic insufficiency [15], such as diabetics or elderly individuals [16]. Severe coronary constriction in response to AVP has been proposed as the mechanism underlying a number of acute ischemic events reported in the earlier literature [17–19]. Although AVP does not seem to cause myocardial ischemia under normal conditions [20], it may well do so under chronic α_1-adrenergic receptor blockade, especially in older patients and in those with various degrees of autonomic insufficiency [15,16].

The experimental evidence suggests that, in the presence of functional baroreflexes, the small elevation in AVP following α_1-adrenergic receptor blockade [13] produces an increase in systemic resistance with a strong reflex suppression of cardiac output [21]. In the absence of an intact sympathetic system, the vascular sensitivity to the vasoconstrictor effect of AVP is enhanced by several orders of magnitude [10,21]. Accordingly, a combination of these factors could explain the increased rates of ischemic cardiomyopathy and/or heart failure in these patients.

Implications for the use of α_1-adrenergic antagonists

What are the implications of the ALLHAT findings? One implication is obviously that α_1-adrenergic antagonists should not be first choice antihypertensives, and this message has already been widely disseminated. These agents are, however, used extensively for their urodynamic properties in patients with benign prostatic hypertrophy, many of whom are older hypertensives (possibly with ischemic heart disease) who prefer to use one drug as monotherapy for both purposes. Indeed, doxazosin and terazosin are probably much more popular for the treatment of prostatic symptoms than for hypertension, and in this setting any cardiovascular adverse effects from their widespread use would most probably go unappreciated.

Competing interests

None declared.

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