

Commentary

Comments on ALLHAT and doxazosin

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Abstract

This commentary has two purposes: to summarize the rationale, design and initial results of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial; and to provide a history of the response to ALLHAT that led to a civil action and a Citizens Petition that was the basis for a public hearing by the US Food and Drug Administration, in May 2001. The author concludes that the results of ALLHAT should be widely disseminated. All clinicians must be warned that initial therapy with doxazosin (and possibly other α_1 blockers) is definitely inferior to low dose diuretic treatment for patients at high risk for cardiovascular disease, such as those enrolled in ALLHAT.

Keywords clinical trial, diuretic, doxazosin, heart failure, hypertension

In April 2000, the first results of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were published summarizing the comparison between two of the four drugs studied (chlorthalidone and doxazosin) as initial monotherapy for hypertension [1]. This prospective, randomized trial was designed to compare a diuretic (chlorthalidone) with long-acting (once-a-day) drugs among different classes: angiotensin-converting enzyme inhibitor (lisinopril); calcium-channel blocker (amlodipine); and alpha blocker (doxazosin). The diuretic had been the mainstay of several previous trials, particularly the Systolic Hypertension in the Elderly Program (SHEP) study [2].

During the first three years of the trial, the Data Safety and Monitoring Committee became aware of different event rates between two groups and, after considerable deliberation, made the decision to discontinue the arm assigned to doxazosin for two stated reasons. One reason was an extremely low likelihood that doxazosin would prove superior to chlorthalidone when the study would be completed as planned. The second reason was a pattern of increased morbid events in comparing doxazosin to the diuretic, which was highly significant on statistical analysis. This pattern is shown in Table 1. While event rates for fatal cardiovascular

disease were similar, there was a disturbing tendency for stroke and a definite trend for heart failure to occur more often in the doxazosin group, than in the group taking chlorthalidone. For heart failure, the curves for event rates diverged quite early in the trial, within the first year, but continued to separate over the three-year period of analysis. ALLHAT continues with ongoing comparisons for amlodipine, lisinopril, and chlorthalidone.

The results of ALLHAT regarding doxazosin were first made public by a presentation at the meeting of the American College of Cardiology, March 2000, and the subsequent publication. Several news agencies published reports of the study, and comments appeared in a few medical journals. There was, however, no action taken by either the United States Food and Drug Administration (FDA) or the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which authored the most recent advisory guideline for the National Heart Lung and Blood Institute [3]. In May 2001, however, after initiation of a class action lawsuit and a Citizens Petition, the FDA held a hearing on the issue. Sidney Wolfe and the author gave presentations recommending that all physicians receive a warning with an interpretation of the ALLHAT results, and

FDA = United States Food and Drug Administration.

ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; HOPE = Heart Outcomes Prevention Evaluation; SHEP = Systolic Hypertension in the Elderly Program.

that the labeling and indications for doxazosin be changed by Pfizer, the company which developed and markets doxazosin as Cardura®. Pfizer's representatives argued that doxazosin is a safe and effective antihypertensive drug, based on their own accumulated studies, with no need for any additional warning or change in labeling. The remainder of this article will summarize the basis for a warning and address the arguments of those who conclude that nothing further needs to be done.

Current treatment of hypertension

There is no longer any doubt that treatment of hypertension is beneficial and prevents stroke, coronary heart disease, and congestive heart failure. This is particularly so for high-risk populations, such as those over 50 years of age, with other risk factors and target organ damage. For the past 20 years, the proliferation of new antihypertensive drug classes has led to speculation (based on various kinds of evidence) that for equal reduction of blood pressure, some classes might be more beneficial than others with regard to effectiveness in preventing cardiovascular disease, and lesser adverse reactions of either minor or major significance. For example, the Heart Outcomes Prevention Evaluation HOPE) trial reported that an angiotensin-converting enzyme inhibitor, ramipril, reduced fatal and nonfatal cardiovascular events in high-risk patients, irrespective of whether or not they were hypertensive [4]. On the other hand, the 'null' hypothesis for treatment of hypertension had been that the benefit of treatment is entirely related to reduction of arterial pressure and that the separate actions of the various drug classes are of no importance [5].

Addressing the issues: the rationale for ALLHAT

While published guidelines suggest uniform treatment for hypertension, practice by individual physicians varies considerably. ALLHAT was conceived and designed to provide meaningful comparisons of three widely used newer drug classes to a 'classic' diuretic, as given in daily practice by primary care physicians for treatment of hypertension [6]. The goal of the trial was to assess cardiovascular mortality and morbidity for stroke, coronary heart disease and congestive heart failure, as an evidence-based guide for clinicians who treat hypertension. ALLHAT is a large multicenter study (44,000 enrolled), with randomization, a double blind design, nearly complete follow-up of enrolled subjects, and other features that qualify it as compelling evidence for clinical decisions.

ALLHAT findings regarding doxazosin

At entry, the baseline characteristics of the doxazosin and chlorthalidone groups in ALLHAT were similar. Ninety percent of both groups had been previously treated and were then changed to their assigned medication. Thereafter, they were treated similarly with addition of a beta blocker or other allowed agents (reserpine or clonidine for second step and

Table 1

Major results of the ALLHAT study

Event	Doxazosin (%)	Chlorthalidone (%)
Coronary heart disease	6.3	6.3
Stroke	4.2	3.6*
Combined cardiovascular disease	25.5	21.8**
Congestive heart failure	8.1	4.5**
Coronary revascularization	6.2	5.2***

Results are presented as a percentage of those entered in each arm, either doxazosin or chlorthalidone. Data from [1]. * $P = 0.04$, ** $P < 0.001$, *** $P = 0.05$.

hydralazine for third step) when needed. In both groups, blood pressure fell significantly from entry levels and remained lower. Despite a uniform goal of treatment for all enrolled, a small difference in systolic pressure was found between the two groups soon after entry and persisted until the doxazosin arm was discontinued. Overall, the doxazosin group had a 2–3 mmHg higher systolic pressure during the trial. Diastolic pressures were equal in the two groups. While a placebo arm was not included (and would have been unethical) there is every reason to accept the view that doxazosin did reduce arterial pressure (i.e. it remains an antihypertensive drug), but slightly less so than the diuretic. The difference of 2–3 mmHg in systolic pressure between the two arms cannot account for doubling of the heart failure rate by doxazosin, compared to the diuretic as shown in Table 1. Furthermore, clinicians treating patients in the two groups were not aware of any difference in response. Adherence to assigned treatment was 10% higher for chlorthalidone, compared to doxazosin over 4 years of observation, but discontinuation of medication was similar for the two groups (20% for chlorthalidone and 19% for doxazosin).

Recommended steps

Is doxazosin (or any other alpha receptor blocker) a dangerous drug? Did the results of ALLHAT reveal drug toxicity or the 'lesser charge' of ineffectiveness? The former status clearly requires a warning and, in some circumstances, may lead to withdrawal of approval. The latter requires widespread information to advise all clinicians who treat hypertension of better and worse strategies. The available studies don't support the concept that doxazosin or alpha blockers have a direct cardiotoxic effect. Rather, clinical research implies that, like prazosin, doxazosin has no sustained hemodynamic benefit for congestive heart failure, due to development of tolerance (i.e. the lack of a sustained hemodynamic effect in those with impaired left ventricular systolic function) [7]. This has led to the suggestion that emergence of heart failure in the doxazosin cohort of ALLHAT was the expression of 'latent' heart failure at

baseline, or soon thereafter, which either had been kept in check by previous treatment or was prevented from appearing by the diuretic or other therapy. The basis for a diagnosis of heart failure was uniform between the two groups [8]. The case-fatality rates for heart failure, however, were also similar for the arms receiving doxazosin or chlorthalidone; once heart failure appeared, its consequences were disastrous. In other words, heart failure as an endpoint in ALLHAT was an important clinical event.

Clinicians who treat hypertension should be aware that doxazosin, certainly as monotherapy, may be ineffective, perhaps little better than a placebo, for patients at higher risk for heart failure. The greater adherence rate for chlorthalidone compared to doxazosin should not be overlooked, as well. In a double blind trial, such a pattern implies that the alpha blocker was, for unknown reasons, less acceptable than the diuretic alternative. This is new and important information from a very large trial, that is not likely to be replicated.

The FDA panel heard the opposing viewpoints on a warning for doxazosin as a result of the ALLHAT trial. They concluded that something should be done, but could not take any further action and, instead, asked for additional analyses. This may be all that current FDA policies allow. There is, however, a compelling mandate emerging from those who see the need for greater safety in the provision of healthcare. Beneficial therapy should be achieved for as many hypertensive patients as possible. If even a small fraction of this large population is given a drug that fails to prevent heart failure, when effective medication might have been prescribed, our system of healthcare is just as deficient as if a more dramatic toxic adverse reaction (such as severe hepatic reactions to troglitazone) had occurred. Results of large and well-conducted clinical trials, such as ALLHAT, must be the basis for optimal healthcare policy.

Competing interests

None declared

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