

Debate

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Back to thiazide-diuretics for hypertension: reflections after a decade of irrational prescribing

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Published: 23 December 2003

Received: 07 August 2003

BMC Family Practice 2003, **4**:19

Accepted: 23 December 2003

This article is available from: <http://www.biomedcentral.com/1471-2296/4/19>

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Abstract

Background: Whether newer antihypertensive drugs, such as calcium channel blockers, angiotensin converting enzyme inhibitors and α blockers are more effective than thiazides and β blockers in preventing coronary disease, has been debated for years.

Discussion: Recently several trials addressing this issue have been finalised, and they provide a convincing answer: the newer drugs are no better than the older ones. In the largest trial to date (ALLHAT), thiazide-type diuretic was found to offer advantages over newer drugs. The medical community should now be capable of reaching consensus, and recommend thiazides as the first line therapy for the treatment of hypertension. Prescribing physicians, cardiologists, drug companies and health authorities are all partly responsible for the years of irrational prescribing that we have witnessed.

Summary: All stakeholders should now contribute in order to achieve what is clearly in the public's interest: implementing the use of thiazides in clinical practice.

Background

The debate over first choice drug for the treatment of hypertension has been intense for years. Opinions have mainly differed with regard to the role of calcium channel blockers, angiotensin converting enzyme inhibitors, α blockers, and more recently the angiotensin II receptor antagonists. These drugs have been shown to effectively lower blood pressure, but until recently their effectiveness with regards to matters of importance, namely health outcomes such as reduction in myocardial infarctions and strokes, had not been proven. In contrast, thiazide diuretics and β blockers have been tested in numerous clinical trials, and have been shown to reduce the risk of cardiovascular disease in people with hypertension.

The effectiveness of hypertension treatment

Hypertension is associated with an increased risk of stroke and coronary heart disease. A review of clinical trials from the 1960s, 70s and 80s showed that the use of thiazides and β blockers had a convincing effect on stroke prevention – the added risk associated with elevated blood pressure was markedly reduced with such treatment [1]. However, the drugs were not as effective at preventing coronary heart disease – although the risk went down, persons on treatment still had a significantly higher risk than persons without hypertension [1]. One hypothesis was that the lack of full effect was caused by detrimental metabolic effects of thiazides and β blockers, e.g. changes in blood lipids or glucose tolerance [2].

Newer is better?

New antihypertensive drugs were introduced in the 1980s: calcium channel blockers, angiotensin converting enzyme inhibitors and α blockers. They were shown to reduce blood pressure effectively and they seemed to be superior to thiazides and β blockers with regards to metabolic effects [2]. Consequently the medical community became rather enthusiastic with the prospect of getting newer and better tools in the prevention of coronary heart disease. The problem was that no clinical trials had been conducted showing that the new drugs did what they were meant to do: prevent people from falling ill or dying. The resulting controversy concerned the interpretation of evidence available at the time. Some physicians argued that the likelihood of the newer being better was strong enough to warrant these drugs to be considered as first line in the treatment of hypertension [3]. Others warned about jumping on new interventions before they had been properly tested, meaning clinical trials with clinically relevant outcome measures such as incidence of stroke, heart attacks and deaths [4].

Clinical trials comparing new and old drugs

It took several years before clinical trials were initiated investigating the effectiveness of the new antihypertensives with regards to disease prevention. Clinical trials of new drugs are usually supported by grants from the pharmaceutical industry, but since the drugs had achieved huge sales without such trials, there was little incentive for the companies to push the issue. For instance, the calcium channel blocker amlodipine became the number one selling antihypertensive few years after introduction to the market – with little or no evidence of its ability to improve people's health. Finally, in the mid-90s and onwards, several clinical trials comparing the effectiveness of thiazides and β blockers with the newer drug classes began [5-11]. Most of the trials were sponsored by the pharmaceutical industry, and had the clear objective of proving that newer is better. The debate over first choice agents continued while the trials were ongoing, but all agreed that the results would provide the answer: are the newer drug classes more effective than thiazides and β blockers at preventing coronary heart disease?

Discussion

Now, many of the trials have been finalised and the results are available [5-11]. Disappointingly, in all but one of these trials [11], neither calcium channel blockers, angiotensin converting enzyme inhibitors nor α blockers performed better than thiazides or β blockers. In contrast, the results of the most extensive study to date (ALLHAT) indicate that chlorthalidone (thiazide-type diuretic) may in fact be superior to the newer drug-classes [6,7]. This study in particular, gives strong weight to the recommendation of choosing thiazides as first choice drugs for hyperten-

sion. All the study results have recently been combined in two meta-analyses, demonstrating that thiazides reduce cardiovascular risk at least as effectively as other antihypertensive drugs [12,13]. In addition, the use of thiazides as first choice therapy will mean substantial cost savings due to their favourable price [14]. Thus, finally, after more than a decade of controversy, the medical community should be capable of reaching a clear consensus: thiazides are, again, the primary agents for the treatment of hypertension [15-17]. However, it should be noted that more than one drug is often needed to control hypertension.

In retrospect

Despite intense debate, e.g. in medical journals, calcium channel blockers, angiotensin converting enzyme inhibitors and α blockers rapidly dominated clinical practice, as evidenced by their market shares in most western countries all through the 1990s. This was, assumingly, a result of effective marketing from drug companies [18,19]. Luckily, choosing calcium channel blockers or angiotensin converting enzyme inhibitors did probably not cause much harm to patients with hypertension who could have taken thiazides or β blockers instead. However, the use of α blockers may have caused some harm to patients as evidenced by the higher incidence of congestive heart failure among patients randomised to doxazosin (α blocker) versus chlorthalidone (thiazide-type diuretic) [7]. In addition, physicians who opted for calcium channel blockers, angiotensin converting enzyme inhibitors or α blockers as first choice drugs for hypertension have put unnecessary strain on health expenses.

What can we learn?

Obviously, prescribing physicians need to rethink their practice, but there are a few additional issues that deserve some reflection. Firstly, a critical attitude towards relying on surrogate endpoints when evaluating medical interventions needs to be re-emphasised [20]. A surrogate endpoint is "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions or survives" [20]. For example, the claim that the α blockers' positive impact on blood lipids would reduce the risk of heart disease was not confirmed, rather the contrary [7]. Effectiveness in terms of blood pressure lowering is another popular surrogate endpoint (see note at end of article), which is of questionable value if the objective is to reduce cardiovascular risk [21]. Secondly, the role of opinion leaders cannot be ignored. During the 1990s cardiologists typically acted as speakers at events hosted by industry where they would preach the superiority of calcium channel blockers, angiotensin converting enzyme inhibitors or α blockers over thiazides and β blockers (author's personal experience). Despite the need to be humble when operating in the light of retrospect, it seems

reasonable to suggest a critical review of the relationship between industry and opinion leaders. Conflicts of interest may be an issue [22], and the methods employed by specialty societies in developing clinical practice guidelines should be examined [23]. Thirdly, this example illustrates how the agenda of the pharmaceutical industry may be contrary to public interests. Profits made from older drugs are minute compared to what may be earned on newer, patent-protected drugs. Finally, health authorities cannot be freed from liability. Both in terms of taking care of the public's health and public money, governmental agencies are obliged to address irrational prescribing patterns.

Summary

Now, the challenge is to implement the use of thiazides in clinical practice. This is not in the interest of drug companies, and they may wish to antagonise initiatives promoting increased use of thiazides (or β blockers) [24]. Opinion leaders, such as cardiologists, should take the lead and promote thiazides as drugs of choice. Continued support for drugs on the basis of surrogate endpoints is unethical now that hard clinical evidence is on the table. Health authorities may find it difficult to identify interventions that will influence physicians' prescribing [25]. Effective interventions such as educational outreach visits are costly, and massive programs such as those run by drug companies, even more so. The available evidence suggests that multifaceted interventions may be effective [26]. Identifying barriers to change and addressing these through tailor made, multifaceted interventions may prove to be an effective strategy [27].

Competing Interests

The author is employed by the Norwegian government, which has a substantial interest in improving professional practice in Norway and in containing the costs of health-care. He is also conducting a trial of implementation strategies for guidelines for the management of hypertension and hypercholesterolaemia.

Note

A figure was meant to be included in this article to illustrate the pharmaceutical industry's use of surrogate endpoints for marketing purposes. A graphic taken from <http://www.norvasc.com>, which also included an intriguing link to the results of the ALLHAT study (ALLHAT-results do not support the use of the drug in the advertisement), could not be reprinted since Pfizer Inc. failed to respond to a request to use their artwork. The author has sent monthly requests per e-mail since 13. August 2003, and has also been in contact with the company per telephone. Despite this, at the time of publication there was still no sign of a decision from Pfizer.

The views expressed in this article are not necessarily in accordance with the views of the Norwegian Directorate for Health and Social Affairs.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

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