Guidelines for Use of Diuretics: A View From a Member of JNC 7

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I appreciated the editorial by Dr Rosendorff[1] concerning the differences between hydrochlorothiazide (HCTZ) and chlorthalidone. It is important to point out that our vision from the year 2012 is much different than it was 10 years ago (2002) when the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) was written. Since then, new information and comprehensive reviews of diuretics have been published.[2–4] However, I would like to provide some context for the discussions of JNC 7 and some of the issues raised in Dr Rosendorff's editorial.

CHLORTHALIDONE VS HYDROCHLOROTHIAZIDE

Dr Rosendorff correctly points out many of the key reasons why chlorthalidone may be superior to HCTZ. He indicts JNC 7 because it did not distinguish the fact that chlorthalidone is not a thiazide diuretic. As a member of the drug therapy writing panel for JNC 7 and the individual responsible for initially creating the drug tables for JNC 5, 6, and 7, I must take responsibility for this lack of clarity.

Both the long version[5] and the express version[6] of JNC 7 used the term *thiazide-type* diuretics to include typical thiazides (eg, HCTZ, chlorothiazide), quinazolines (eg, metolazone), the indoline (indapamide), and the phthalimidine derivative (chlorthalidone). This long-standing term was used to acknowledge that not all diuretics, especially chlorthalidone, are thiazides. It is unfortunate that the JNC 7 report could not go into more detail about the chemical, pharmacologic, and pharmacodynamic differences between these agents. But, it should be appreciated that the JNC 7 long-version manuscript was already 181 pages in length and nearly every issue could have benefited from more in-depth discussion. More importantly, the audience for JNC guidelines is composed of busy, practicing clinicians, and focus group discussions with them determined that they prefer a succinct document that gets to the point of what to do, thus the need for JNC 7 Express. Long erudite discussions, while interesting, would most likely not be read by them. There was a great deal of overlap between members of JNC 7 and the National High Blood Pressure Education Program Committee. Members of both committees frequently heard presentations about key studies that were yet to be published during meetings in 2001 to 2002. The majority of scientific evidence at that time was with two diuretics: HCTZ and chlorthalidone. I recall my concern about the differences between these drugs including pharmacology and hard outcomes based on the retrospective review of the Multiple Risk Factor Intervention Trial published 12 years earlier.[7] The Committee discussed the fact that there were small studies that compared HCTZ with chlorthalidone on blood pressure end points but that evidence was insufficient to rise to the level required by JNC 7 since we were concerned with hard end points.[8–11]

Chlorthalidone had been in the top 200 most prescribed drugs when I was training in the 1970s but had appeared to fall off the face of the earth by 2002. Members of JNC 7 did appreciate the differences between HCTZ and chlorthalidone. After all, this was one major reason that chlorthalidone was the drug used in most of the major trials supported by the National Heart, Lung, and Blood Institute (NHLBI) dating back to the 1970s, culminating with the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in 2002.[12–15] While the Committee discussed comparisons of diuretics, it intrigued me that there was virtually no discussion of these issues in the literature between 1985 and 2002. It so happened that I sat next to Dr Jerome Cohen during these sessions and I asked whether he would be interested in writing a paper on differences between HCTZ and chlorthalidone. Following the publication of JNC 7, we wrote a paper with Dr Michael Ernst.[16] Dr Ernst then conducted several studies that nicely demonstrated the clear differences with chlorthalidone that Dr Rosendorff discusses.[17–20]

However, the question as to why HCTZ may not have performed well in some studies may very likely be due to the fact that evidence-based dosages were not used.[21] Studies that found HCTZ to be superior to placebo or other agents used 25 mg to 100 mg daily.[3,22–24] Dr Rosendorff mentions the inferior effects of HCTZ in the Second Australian National Blood Pressure Study (ANBP-2),[25] but the deficiencies of this study have been reviewed by others. Briefly, this study had far fewer outcomes than other studies such as ALLHAT and Systolic Hypertension in the Elderly Program (SHEP). The effect was apparent only in men, and the accepted significance level was $P=.05$. Most importantly, doses of HCTZ were not specified in the paper and doses were adjusted by family practitioners. We know from extensive practice data that the doses of HCTZ most frequently used are 12.5 mg to 25 mg daily, so it is likely that these are the doses that were used in ANBP-2. Thus, the doses of HCTZ used in this study probably were not evidence-based.

Dosage is important, but I also think duration of action is critical. Protecting patients through the entire 24-hour dosing interval has increasingly been shown

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to reduce cardiovascular risk.[24] HCTZ does not reliably reduce blood pressure throughout the entire 24-hour interval for all patients.[17] In fact, in the 1970s, it was common to use HCTZ twice a day and one must ask whether that is the more appropriate way to dose the drug for many patients.

My personal feeling is that chlorthalidone is superior to HCTZ for both blood pressure and hard outcomes,[7,26,27] although some analyses found no difference between chlorthalidone and other diuretics.[28] While there are plenty of intriguing data to support the superiority of chlorthalidone over other diuretics, the fact is that members of JNC 7 simply did not have sufficient evidence from randomized controlled trials with hard outcomes to prove any differences between these two drugs. Such evidence is clearly what is needed to craft guidelines. The fact is, we still do not have sufficient evidence in 2012 to suggest that we should avoid using HCTZ.

NEW-ONSET DIABETES

Another key issue raised by Dr Rosendorff was new-onset diabetes associated with diuretics. This was another topic that came up in 2002 during the JNC 7 discussions. I recall that there seemed to be a general lack of appreciation for the relationship between diuretics, hyperglycemia, and hypokalemia at that time. This relationship had been known since the early 1960s and I first studied this issue in a course on adverse drug reactions as a student in the late 1970s.[29–31] Dr George Bakris and I discussed the critical nature of this issue and decided to search the literature and conduct a systematic review. We elicited the help of our respective postdoctoral fellows, Dr Jay Garg and Alan Zillich, and we demonstrated a strong relationship between hypokalemia and elevations in glucose.[32] That information eventually resulted in an NHLBI working group report that called for more research on this issue.[33] Several studies have been conducted to confirm these relationships and possible mechanisms.[34–38] However, others have not found an association between hypokalemia and hyperglycemia.[39,40] Of course, if there is a strong relationship between hypokalemia and hyperglycemia, strategies to maintain serum potassium concentrations would be important (actually total body composition is more important). Once again, the JNC 7 panel appreciated the issues related to new-onset diabetes and diuretic therapy. But, we must remember that a great deal of information has been published since December 2002, when the JNC 7 document writing was completed.

Regardless, I strongly advocate for maintaining serum potassium in the high normal range. The best way to do that is with combinations of an angiotensin-converting enzyme inhibitor,[41] an angiotensin receptor blocker, a potassium-sparing agent combination,[42–46] or potassium supplementation.[47]

The bigger question is whether new-onset diabetes associated with diuretics contributes to cardiovascular events. The evidence for harm from one small study had very few end points.[48] These findings were not supported by large, prospective, randomized trials.[49–52] In fact, in the SHEP trial, chlorthalidone use in diabetics was associated with a 2-fold greater reduction in cardiovascular risk when compared with nondiabetics.[49] So, despite the fact that we wish to avoid new-onset diabetes in all patients, the evidence suggests that these patients still receive major cardiovascular benefit with a diuretic should diabetes develop.

SUMMARY AND IMPORTANT CONSIDERATIONS

This editorial is not meant to criticize Dr Rosendorff's main message. Rather, I wish to lend some perspective on the deliberations going on 10 years ago at the time JNC 7 was written as well as some of the constraints placed on guidelines due to journal page limitations.

Regardless of our opinions, the fact is that the majority of hypertensive patients benefit from diuretic therapy either as first- or second-line therapy. With that in mind, it is critical to properly use these agents. Some important considerations include:

- Understanding that chlorthalidone is twice as potent as HCTZ and has a much longer duration of action.
- Using evidence-based dosing: For HCTZ, that means 25 mg to 50 mg daily and for chlorthalidone, 12.5 mg to 25 mg daily. Lower doses may compromise the effects to reduce cardiovascular outcomes.
- Looking carefully at whether a patient taking HCTZ who has access to 24-hour ambulatory blood pressure monitoring has appropriate dipping status and blood pressure coverage at the end of the dosing interval (eg, early morning before the next dose). If there is evidence that the 24-hour blood pressure control is not optimal and you choose to keep the patient on HCTZ, consider twice-daily doses.
- Maintaining normal serum potassium levels. The most effective ways to maintain potassium levels includes lower sodium intake or combined treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or potassium-sparing diuretic. Consider spironolactone[42,43] or amiloride[44,45,53] with chlorthalidone or HCTZ in patients with resistant hypertension, as this is a particularly potent combination.

It is important to consider that not all evidence and discussions from guideline committees yield evidence with sufficient strength to make it into the final reports. It is unfortunate that the most recent US hypertension guidelines are now nearly 10 years old. However, we must consider that lag when we comment on the strengths and weaknesses of guidelines.

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