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Hypertension News
This Issue: Sense and Nonsense of HCTZ

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HYPERTENSION *news*

Sense and Nonsense of HCTZ

Hypertension News is a physician bulletin providing updates and information on hypertension services at **St. Luke's** and **Roosevelt Hospitals** which may benefit your practice and your patients.

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Ever since the first Joint National Committee (JNC) in 1997 recommended a "thiazide-type diuretic" as first-line therapy for hypertension, every following JNC (II, III, IV, V, VI and 7) reiterated these recommendations. It is therefore not surprising that Hydrochlorothiazide (HCTZ) has become by far the most commonly prescribed antihypertensive drug in the United States. In 2008, 47.8 million prescriptions of HCTZ and 87.1 million prescriptions of HCTZ in combination were written in the US. Of these prescriptions only 3% were for a dose of HCTZ exceeding 25mg. Thus, the great majority of HCTZ prescriptions are for 12.5 or 25mg once a day.

Given the strong recommendation by all the JNCs, most physicians take the safety and efficacy of HCTZ for granted. We recently dared to scrutinize the halo surrounding this venerable drug that has been around for more than half a century. We did a review of all randomized trials assessing 24-hour blood pressure with HCTZ in comparison with other antihypertensive drugs[1]. We found a total of 19 studies with over 1,400 patients. To our great surprise we found a rather paltry antihypertensive efficacy. In this large database, HCTZ in the dose of 12.5-25mg decreases 24-hour ambulatory blood pressure by a meager 6.5/4.5mmHg. This was distinctly inferior in head-to-head studies to the decrease in blood pressure with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and calcium channel blockers (CCBs). This brings us to conclusion number 1.

Conclusion 1:

HCTZ is an inferior antihypertensive drug.

The JNC 7 states, "In trials comparing diuretics with other classes of antihypertensive agents, diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension." What then are the data showing that HCTZ in the dose of 12.5-25mg reduces major cardiovascular events? Unfortunately, there are no such data. All studies with HCTZ were done at the much higher dose or in combination with a potassium sparing diuretic. Thus, there is no evidence showing that HCTZ in the dose of 12.5-25mg reduces heart attack and stroke. This brings us to conclusion 2.

Conclusion 2:

Hydrochlorothiazide in its usual dose has not been shown to reduce morbidity and mortality in hypertension.

In higher doses HCTZ has been shown to increase the risk of cardiac arrest in a dose-dependent way[2]. Compared to HCTZ 25mg daily, 50mg daily has been reported to increase the risk of primary cardiac arrest (OR 1.7) and 100mg was associated with an even larger increase in risk (OR 3.6)[2]. One may appropriately ask at this juncture what then was the evidence from which the statement of the JNC 7 is originating from. The thiazide diuretics shown to reduce morbidity and mortality in hypertension are chlorthalidone in SHEP[3] and ALLHAT[4] and indapamide in HYVET[5]. Both of these diuretics have been shown to exhibit differences when compared to HCTZ to the extent that an extrapolation from indapamide or chlorthalidone data to HCTZ is not acceptable. This brings us to conclusion 3.

Conclusion 3:

Not all so-called "thiazide diuretics" are created equal.

Numerous fixed combinations with HCTZ and beta-blockers, HCTZ and ACE inhibitors and HCTZ and ARBs are available. In most of these combinations HCTZ is used in the dose 12.5-25mg. There is little doubt that in combination with an inhibitor of the renin angiotensin system, HCTZ enhances the antihypertensive response. However, the recent ACCOMPLISH[6] in which benazepril/HCTZ was compared with benazepril/amlodipine in over 11,000 patients had to be stopped prematurely because there was a 20% reduction in morbidity and mortality in the amlodipine/benazepril arm when compared to the HCTZ/benazepril arm. Since blood pressure was lowered to the same extent in both treatment arms (as documented by 24-hour ambulatory blood pressure monitoring), this would indicate that over and above blood pressure reduction either amlodipine is beneficial or HCTZ is detrimental[7]. This leads us to conclusion 4.

Conclusion 4:

Even in combination with an ACE inhibitor, HCTZ is inferior to a CCB.

When the authors of JNC 1-7 were recommending "thiazides" as first-line or preferred therapy, they were fully aware that to 99.9% of practicing physicians in the US this did not mean chlorthalidone or indapamide but meant very simply, HCTZ in the dose of 12.5-25mg once a day. Clearly these JNC recommendations must be considered deceptive. For two decades, ever since the MRFIT trial[8], we have known that chlorthalidone might be better in reducing morbidity and mortality than HCTZ.

In conclusion, since outcome data at the usual daily dose of 12.5-25mg is lacking and antihypertensive efficacy is paltry, HCTZ is an inappropriate first-line drug for hypertension. If a "thiazide-type" diuretic is indicated, either indapamide or chlorthalidone should be selected.