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HYPERTENSION *news*

Thiazides: Myths, Fables, and Fairytales

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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Definition

The drugs usually considered to belong to the so-called thiazide class are Hydrochlorothiazide (HCTZ), Chlorthalidone, Indapamide, Chlorothiazide, Bendroflumethiazide, Hydroflumethiazide, Polythiazide, Metolazone, Trichlormethiazide, and Quinethazone. By far the most commonly used among them is HCTZ. In fact, HCTZ is the most commonly used drug worldwide.[1] More than 150 million prescriptions are written every year in the US alone. This is perhaps not surprising given that ever since the first Joint National Committee (JNC I) in 1977[2] every subsequent JNC has recommended a thiazide or a thiazide-like diuretic as first-line therapy for the treatment of hypertension. For practicing physicians, the JNC's recommendation of a "thiazide" or a "thiazide-like diuretic" invariably meant HCTZ and not Chlorthalidone or Indapamide or any other thiazide diuretic. This monopoly of HCTZ is puzzling given that the majority of the outcome data with thiazides were collected with Chlorthalidone and Indapamide.

Outcome data with thiazides

What then are the data with HCTZ showing a reduction in heart attack and stroke? A thorough survey of the available literature shows that for HCTZ in its most commonly used dose of 12.5-25 mg once-a-day there are no such data. The only outcome data that can be found are with higher doses of HCTZ, with HCTZ in fixed combination with other drugs, or with HCTZ in combination with a potassium-sparing drug.[3] However, no morbidity or mortality data have been reported for HCTZ alone at the dose of 12.5-25 mg once-a-day.[1] We clearly should remember that HCTZ with a potassium-sparing drug cannot be considered as equivalent to HCTZ alone. The best example documenting the detrimental effect of hypokalemia was the SHEP study in which patients who had significant chlorthalidone-induced hypokalemia lost all morbidity and mortality benefits stemming from the reduction in blood pressure.[4] In SHEP, hypokalemic patients did not fare better than those on placebo despite a significant blood pressure reduction.

Deceptive Promotion by the National Heart Lung and Blood Institute (NHLBI)

In the aftermath of the ALLHAT study, the NHLBI made an extensive effort to promote thiazides. More than 100 "educators" were sent out to practicing physicians promoting "thiazide-type diuretics" in dinner talks and Grand Rounds all over the USA.[5] Although the ALLHAT study used Chlorthalidone only, the NHLBI-related effort uncritically promoted "thiazide diuretics", which resulted in an increased prescription rate of HCTZ and not Chlorthalidone. As Kurtz pointed out,[6] by placing non-thiazide diuretics including Chlorthalidone in a class labeled "thiazide diuretics," the JNC 7 tacitly encouraged the belief that Chlorthalidone and Hydrochlorothiazide are equivalent with respect to their therapeutic effects.

Not all thiazides are created equal

A variety of differences among thiazides have been documented in head-to-head comparisons. Clearly, HCTZ can not be considered equivalent to either one of the two diuretics with solid outcome studies, i.e., Indapamide and Chlorthalidone. Of note, in its commonly used dose of 12.5-25 mg a day, HCTZ is one of the weakest antihypertensive drugs available. In head-to-head comparison it has been shown to be inferior to ACE inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers.[7] Perhaps even more worrying than the weak antihypertensive efficacy is the fact that with HCTZ there is a 5/2 mm Hg difference between office blood pressure and 24-hour ambulatory blood pressure.[7,8] HCTZ lowers blood pressure significantly better during the daytime (when the patient is seen in the physician's office) than at night. Assessing the antihypertensive efficacy of HCTZ by office blood pressure measurements is therefore deceptive and is prone to lull physicians and patients into a false sense of security. In contrast, for both Indapamide and Chlorthalidone solid ambulatory blood pressure data have been put forward documenting a sustained blood pressure reduction over a full 24-hour period.[9,10,11]

Blood pressure variability and stroke prevention.

Another risk factor to be considered in this context is blood pressure variability. Rothwell et al reported visit-to-visit blood pressure variability to be a significant risk factor for the occurrence of stroke.[12] The drug classes best suited to reduce variability seem to be the calcium channel blockers followed by the thiazide/diuretics and then the ARBs, ACE inhibitors, beta-blockers etc.[13] No blood pressure variability data are available with HCTZ. However, in a recent multicenter, randomized, double-blind, placebo-controlled study of more than 500 patients, Zhang et al[11] showed that only Amlodipine and Indapamide were associated with a significant reduction in blood pressure variability whereas no reduction in blood pressure variability was seen with Candesartan or placebo.

Is dawn breaking?

Given the deceptive information that was put forward by the Joint National Committee over the years, it is reassuring that recently some voices can be heard attempting to set the record straight. Evidently, the data are compelling enough to differentiate Indapamide and Chlorthalidone from HCTZ. Thus, the new British Hypertension Guidelines state "If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlorthalidone (12.5-25 mg once-a-day) or indapamide (1.5 mg modified release or 2.5 mg once-a-day) in preference to a conventional thiazide diuretic such as bendroflumethiazide or HCTZ."[14] These new recommendations are reassuring and we can only hope that the JNC 8, which it is to be hoped will become available later this year, will also see the light and separate the wheat from the chaff.