Thiazide diuretics in hypertension

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Topics:
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The use of diuretics (and beta-blockers) to treat hypertension has known a dramatic decline since the early 1980’s through to the early 1990s with the introduction of ACE-inhibitors and calcium channel blockers. However, thiazide diuretics are still a first line option to treat arterial hypertension, due to their efficacy and cost-effectiveness profile. We have presented major trials on this subject in this review.

Background

Thiazide Diuretics have been used since the late fifties in the treatment of hypertension and remain one of the most important group of drugs used to reduce blood pressure, due to their efficacy and cost-effectiveness profile.

The use of diuretics (and beta-blockers) to treat hypertension has known a dramatic decline since the early 1980’s through to the early 1990s with the introduction of ACE-inhibitors and calcium channel blockers. Thiazides were used in much higher doses then and concerns were raised regarding their metabolic effects (1). Nevertheless, in this review we will try to demonstrate that thiazide diuretics are still a first line option to treat arterial hypertension.

Clinical Pharmacology

The onset of action occurs after 2 to 3 hours for most thiazides, with little natriuretic effect occurring beyond 6 hours (2). The bioavailability and plasma half-lives explain the differences in pharmacokinetics of different compounds, and hydrochlorothiazide (HCTZ), which has the best profile, was elected as the paradigm of thiazides for the treatment of hypertension. Its half-life of 8 to 12 hours permits effective once daily doses. Among thiazides,

- Chlorthalidone is especially long-acting, with an half-life of 50 to 60 hours, and is twice as potent as HCTZ. Initial decreases in blood pressure (BP) are attributed to the reductions in extracellular fluid and plasma volumes. The persistent antihypertensive effects are due to an overall reduction in systemic resistance. Sodium restriction enhances the therapeutic response to thiazides.
- Thiazides are considered ineffective when the glomerular filtration rate decreases below 30 to 40 ml/min. Metolazone, a quinazoline derivative is an exception among thiazides because it retains its efficacy in patients with renal insufficiency or other diuretic resistant states (2). Metolazone should be reserved for use in combination with loop diuretics in patients with volume overload.
• Indapamide is a thiazide-type diuretic derived from chlorosulphonamide. Indapamide appears to inhibit the Na+/Cl- cotransporter in the cortical diluting segment of the proximal portion of the distal tubule in a manner similar to the metolazone (3). At therapeutic dosages indapamide has only mild diuretic activity and the primary antihypertensive effect is through a direct vasodilatory effect. The efficacy of indapamide in the treatment of hypertension has been examined in large, randomized, multicenter trials with thousands of patients (4-6). In these trials indapamide was well tolerated and reduced BP as effectively as therapeutic dosages of amlodipine, candesartan, enalapril or HCTZ.

Safety and Adverse Effects

Thiazides can reduce the excretion of calcium and uric acid and therefore increase their plasma levels. As well, they increase potassium and magnesium excretion, leading to hypokalemia and hypomagnesemia. Hypokalemia seems to be implicated in the pathogenesis of thiazide-induced dysglycemia. We will come to this topic later in this paper. New onset diabetes has been reported in patients receiving thiazides. According to Carter et al (7) the use of thiazides over several years may lead to an excess of 3 to 4% of new cases of diabetes.

Chlorthalidone superior to Hydrochlorothiazide

Most major clinical trials used either HCTZ or chlorthalidone. The trial sponsored by the National Heart, Lung and Blood Institute (ALLHAT) used chlorthalidone on the belief that it might have advantages related to its longer duration of action. In addition, the data from Multiple Risk Factor Intervention Trial (MRFIT) suggested that chlorthalidone could confer mortality benefits over HCTZ.

When MRFIT was begun, either chlorthalidone or HCTZ could be used according to the experience of each clinical centre. After 7 years the Policy Advisory Board recommended that all subjects be given chlorthalidone because the trend of mortality was unfavourable in the 9 clinics using HCTZ compared to the favourable trend in the 6 clinics using chlorthalidone (8). In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), conducted between 1994 and 2002, chlorthalidone was chosen to be compared with a calcium channel blocker (CCB-amlodipine) and an ACE-inhibitor (lisinopril). Results, after a mean follow-up of 4, 9 years, showed that a thiazide –type diuretic was superior in preventing major forms of cardiovascular disease (9).

Carter and co-workers on a literature search from 1960 to 2003 evaluated the pharmacokinetic and blood pressure lowering effects of both drugs. They found that chlorthalidone is 1.5 to 2.0 times as potent as HCTZ, and a much longer duration of action (3). A more recent paper of the same group (10) compares the antihypertensive effects of both drugs appealing to ambulatory and office blood pressure. The results show that chlorthalidone is more effective in lowering systolic blood pressure measurements than HCTZ, as evidenced by ambulatory BPs, due primarily to the reduction of night time systolic BP. This differences were not apparent with office BP.

Main Clinical Trials

There is a consensus that large randomized trials measuring fatal and non-fatal events represent the strongest type of evidence available (11). ALLHAT was designed to address the issue of which class of drugs should be the first step therapy for hypertension. In the early 90s, that was a very timely question due to the recent introduction of new groups of drugs for hypertension. The overall findings of the trial showed that CHD risk was not improved for any of the newer agents compared with the diuretic treatment represented by chlorthalidone, and that total mortality was also similar for the 4 groups (9).
However, diuretic based therapy was superior to CCB, ACE-inhibitor and alpha-blocker in preventing 1 or more major forms of CVD, including heart failure and, in some cases, stroke. The observed rates of heart failure were higher with amlodipine and lisinopril than with chlorthalidone. Some authors suggest that the longer duration of action of chlorthalidone may explain the advantage in CVD prevention over HCTZ.

The Second Australian National Blood Pressure Study (ANBP2) compares diuretic-based (HCTZ) with ACE-inhibitor-based (enalapril) antihypertensive treatment. A total of 6083 participants, aged 65 to 84 years, were followed for 4 years (11). The results favoured the ACE-inhibitor group, with a decrease in cardiovascular events and myocardial infarction, and an equal number of strokes, despite a similar reduction of blood pressure. The results of ANBP2 were published less than 1 year after ALLHAT and left the medical community confused such that Frohlich asked in an editorial (12): What are we to believe? In his comment he emphasised the difference between the study drugs: ANBP2 used HCTZ as the diuretic, whereas ALLHAT used chlorthalidone. The two trials used vastly different definitions of primary and secondary outcomes. The characteristics of the two populations were different with 35% of blacks in ALLHAT and only 5% in ANBP2. He concludes that the 2 studies are not comparable, and that the choice of appropriate therapy should be made according to the specific problems of the patient.

At the same time an important meta-analysis, using a new methodology, network meta-analysis, which combines direct and indirect evidence to better define risks or benefits, was presented by Psaty et al (13). Data were combined from 42 clinical trials that included more than 190,000 patients randomised to 7 major treatment strategies, including placebo. For all outcomes low-dose diuretics were superior to placebo: CAD; congestive HF; stroke; CVD events; CV mortality. None of the first-line treatment strategies – beta-blockers, ACE-inhibitors, CCB, alfa-blockers and angiotensin receptor blockers (ARB) – was significantly better than low-dose diuretics for any outcome. The authors conclude that low-dose diuretics are the most effective first-line treatment for preventing cardiovascular disease morbidity and mortality.

**New Onset Diabetes and Hypokalemia with Thiazides**

Recent epidemic of obesity and diabetes raised again the problem of adverse effect of thiazides, namely the metabolic effects. In the ALLHAT, among the patients without diabetes mellitus (DM) at baseline, the percentage of incident DM was 11% in the chlorthalidone group, 9.3% in the amlodipine group and 7.8% in the lisinopril group, respectively. In spite of that higher incidence of DM with the thiazide it did not translate into any disadvantage for the diuretic arm during the mean follow-up of 4.9 years (1).

In a recent network meta-analysis Elliot and Meyer (14) undertook a systematic review up to Sept 2006 and identified 22 clinical trials with more than 143,000 participants without DM at randomization. The main outcome was the proportion of patients who developed DM. The odds ratio for incident DM was, with ARBs and ACE-inhibitors, inferior to placebo; it was superior with CCBs(1.05), beta-blockers(1.25) and diuretics(1.34) p=0.001. The authors conclude that the association of antihypertensive drugs with incident DM is lowest for ARB and ACE-inhibitors followed by CCB, placebo, beta-blockers and diuretics in rank order. However, it must be recognized that in a typical hypertensive population the great majority of incident DM that occurs while taking a thiazide is not drug induced but is due to typical causes of type 2 diabetes.

From ALLHAT data regarding incident DM at 4 years, its fraction can be estimated as 83% (1). Messerli et al (15) in his controversy with Cutler and Davis (Circulation, May 20,2008) accepts that new onset diabetes (NOD) associated with diuretics may be reversible on the discontinuation of the
diuretic. Thus treatment withdrawal could potentially separate the drug induced NOD from spontaneously occurring NOD (15).

The evidence on whether the development of dysglycemia with any antihypertensive drug treatment produces adverse CV effects is mixed (14). Both ALLHAT and SHEP (Systolic Hypertension in the elderly Program) (16), the largest and longest follow-up studies, show no significant adverse CV events from new diuretic-associated diabetes. In ALLHAT diuretic-based therapy still afforded major CV benefits compared with amlopidine and lisinopril, even in patients with diabetes. Overall there was no consistent evidence from observational studies that thiazide diuretics increased the risk of DM among hypertensive patients (7).

The difficulty in establishing a clinical connection between diuretic treatment and NOD is the absence of a link between diuretics and hyperglycemia. Zillich et al (17) conducted a literature search from 1966 to 2004 to identify clinical trials using thiazides where the metabolic effect on potassium and glucose are reported. The data collected from 59 clinical trials establish a correlation coefficient of 0.54 (P<0.01) thus suggesting that thiazide-induced hypokalemia is associated with increased blood glucose. Experimental work indicate that low plasma potassium could impair insulin secretion and thereby increase plasma glucose (18). Treatment of thiazide induced hypokalemia may reverse glucose intolerance and prevent diabetes (17). Hypokalemia can be prevented or treated with K+ supplements or combinations of thiazides with K+ sparing diuretics (amiloride and triamterene) and aldosterone-receptor antagonists (eplerenone or spironolactone). On the other hand it has been known, for many years, that when an ACE-inhibitor is added to a thiazide, the metabolic effects of the diuretic are minimized. In all, the cause of diabetes epidemic is increasing overweight/obesity and physical inactivity. Most NOD in diuretic treated patients is not diuretic induced. Cases can likely be prevented by avoiding significant potassium depletion – Cutler and Davis (1).( Controversy with Messerli et al – Circulation, May 20, 2008).

ACCOMPLISH Trial

In the ACCOMPLISH trial (19) (Avoiding CV events through combination therapy in patients living with systolic hypertension) 11,506 patients with hypertension who were at high risk for CV events, were randomised to receive treatment with either benazepril plus amlopidine or benazepril plus HCTZ. The hypothesis to test was if the association of a ACE-inhibitor plus a CCB would be better in reducing CV events than ACE-inhibitor plus a thiazide diuretic. The trial was prematurely terminated after a mean follow-up of 36 months, when the boundary of the prespecified stopping rule was exceeded. There were 552 primary-outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-HCTZ group (11.8 %), representing a relative risk reduction of 19.6% (P<0.001). The authors concluded that Ace-inhibitor+CCB was superior to ACE-inhibitor+HCTZ in reducing CV events in patients with hypertension who were at high risk for such events. More recently the results of renal outcome have showed that benazepril +amlodipine slows the progression of nephropathy to a greater extent (20). In the editorial by Chobanian(21) the use of HCTZ instead of chlorthalidone as diuretic is emphasized and the authors considered that the dose of HCTZ used (averaging 19mg/day) could not provide 24 hours BP control. The experimental evidence that ACE-inhibitors and CCB have vasoprotective effects may be important, as well. This property is not shared by diuretics, but its clinical relevance is uncertain. Finally Chobanian stresses that the most important treatment issue is to reduce BP to goal levels. How this is achieved is less important.

The preference for diuretics in the management of hypertension has been challenged in light of the results of the ACCOMPLISH Trial. The notion that newer agents have beneficial blood pressure-
independent effects has been the basis of their marketing. This cardioprotective or vasoprotective
effects has been also mentioned to explain the effects of ramipril in the HOPE trial (22). We know,
today, that the reduction of blood pressure “per se” explains the main benefits in terms of CV
morbidity and mortality. The best explanation for the paradoxical results of ALLHAT and
ACCOMPLISH trials is the use of different diuretics – Chlorthalidone and HCTZ, respectively
(23).
The results of 10 years follow-up of the ALLHAT population, presented at the American Heart
Association Meeting, November, 2009, showed that amlodipine and lisinopril treatments were not
superior to Chlorthalidone-based treatment in preventing major CV events (24).

In a recent (2009) reappraisal of European guidelines on hypertension management (25), a
European Society of Hypertension statement, confirms that major antihypertensive drug classes do
not differ significantly for their overall ability to reduce BP in hypertension. They also emphasize
that cardiovascular protection by antihypertensive treatment substantially depends on BP lowering
per se, regardless of how it is obtained. These two points are also the conclusions of a meta-analysis
by Law and co-workers from the London School of Medicine (26). Their analysis included 147
randomised clinical trials published between 1966 and 2007 and the conclusion is categoric: “All
the classes of BP lowering drugs have a similar effect in reducing CHD events and stroke for a
given reduction in BP, so excluding material pleiotropic effects”

In CONCLUSION we can cite Norman Kaplan in a recent editorial in “Hypertension”, November
2009: “Appropriate use of diuretics can still be a safe and effective way to treat hypertension” (27).

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<td>2. Hyperuricemia</td>
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<td>3. Dysglycemia. Diabetes</td>
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<td>3. The ALLHAT trial demonstrated, for the first time, the superiority of chlorthalidone over ACE-inhibitors and Calcium Channel Blockers in patients with Diabetes and Chronic Renal Disease.</td>
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<td>4. Chlorthalidone is more potent and has a longer duration of action than hydrochlorothiazide, and should be preferred, alone or in combination, for the management of hypertension.</td>
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Adapted from Fuchs FD, ref.23
Table 4. Thiazides in hypertension - CHOICE OF ANTIHYPERTENSIVE DRUGS

1. The main benefits of antihypertensive therapy are due to lowering of blood pressure, per se, regardless of how it is obtained.

2. Major antihypertensive drugs classes do not differ significantly for their ability to reduce blood pressure

3. Each drug class has contra-indications as well as favourable effects in specific clinical settings. The choice of drugs should be made according to this evidence.

References

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27. Kaplan NM. The choice of thiazide Diuretics. Why Chlorthalidone may replace Hydrochlorothiazide. Hypertension 2009;54: