THIAZIDE DIURETICS IN THE MANAGEMENT OF HYPERTENSION

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ABSTRACT

Hypertension is highly prevalent in Canada, affecting more than 20% of all adults.[1] Thiazide diuretics have been shown in numerous studies to be effective agents for controlling blood pressure and reducing cardiovascular disease and death in hypertensive patients.[2] Thiazide diuretics are recommended as initial first line therapy for uncomplicated hypertension in the 2003 Canadian Hypertension recommendations.[3] However, these agents are underutilized and in Canada, the proportion of persons with hypertension treated with diuretics is declining.[4] To improve understanding of thiazide diuretic use, this document outlines the clinical pharmacology of thiazide diuretics, evidence for effectiveness in treating hypertension, as well as the side effects and controversies surrounding their use.

Thiazide diuretics (hydrochlorothiazide, chlorthalidone) are one of three major classes of diuretics. They act primarily at the distal convoluted tubule and connecting segments of the nephron by inhibiting the Na-Cl electro-neutral co-transporter. This inhibition leads to the initial diuretic effect causing a reduction in plasma volume and cardiac output.

Because the distal convoluted tubule handles less than 5% of the filtered sodium load within the nephron, this diuretic activity is only modest. With long- term usage, the plasma volume and cardiac output partially return to normal and the systemic vascular resistance decline.[5]. This fall in systemic vascular resistance is one of the major mechanisms of blood pressure lowering and may be related to potassium channel activation.[6] The blood pressure lowering effect of low dose thiazides may be apparent as early as 48 hours, but may take longer than 8 weeks for the full antihypertensive effect.[7] The dose response to thiazides diuretics is not well established. However, there appears to be increasing antihypertensive effectiveness at doses up to but exceeding those of low dose diuretics (12.5-25 mg/day of hydrochlorothiazide) in patients with lower stages of hypertension and normal renal function.[8-10]

Low dose chlorthalidone has been used in major clinical trials 12.5-25 mg/day), [15] is about 30-40% more potent on a mg per mg basis than hydrochlorothiazide, and has a very long duration of action. However, the utility of chlorthalidone is very limited in Canada because currently, the smallest tablet available is 50 mg making low dose therapy awkward at best. High doses of thiazide diuretics or high potency loop diuretics may be required in resistant hypertension and renal dysfunction.

When combined with other antihypertensive drugs such as ace inhibitors and beta-blockers they produce a synergistic blood pressure lowering effect.[11-13] Reduction in blood pressure with calcium channel blockers may not be additive.

EVIDENCE FOR EFFECTIVENESS

Placebo controlled trials

Earlier studies on hypertension were placebo controlled and from these high quality long-term studies, thiazide diuretics were strongly associated with reduced morbidity and mortality. From a meta- analysis of these

trials, low dose thiazide diuretics have shown a 10% reduction in risk of overall mortality (95% CI, 16% to 4%), 29% reduction in risk of stroke (95%CI: 37% to 19%), 49% decrease in congestive heart failure (95%CI: 58% to 38%) and 24% reduction in rate of cardiovascular disease events compared to placebo (95% CI: 17% to 31%).[2]

Low vs. high dose thiazides

When comparing high dose diuretics versus low dose diuretics, Psaty et al[14] found that although both led to similar reductions in blood pressure, there were differences in effect on cardiovascular disease event rates. While both high and low dose diuretics were associated with reduced rates of stroke and cardiovascular mortality, only low dose diuretics were associated with an additional reduction in coronary heart disease and total mortality. Based on this additional benefit, low dose diuretics should be used when treating hypertension.

Thiazides vs. other antihypertensives

More recent studies have compared newer classes of antihypertensives with older established agents. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[15] a randomized controlled trial of 42 418 high risk hypertensive patients compared the efficacy of angiotensin converting enzyme inhibitors, calcium channel blockers, alpha blockers to low dose thiazide diuretics (chlorthalidone 12.5-25 mg/d). In this landmark trial, there were no significant differences in rates of coronary heart disease events and total mortality between the three classes and thiazide diuretics. This finding was also consistent across both men and women, white and black participants and those with and without diabetes mellitus.

A recently published meta analysis of 42 trials including ALLHAT and 192 478 patients found that none of the first line treatment strategies: beta blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, alpha blockers and angiotensin receptor blockers, were significantly better than low dose diuretics.[2]

Therefore, from numerous placebo and active controlled trials, low dose thiazide diuretics have an established role as a first line therapy in treating hypertension. (See Table 1).

TOLERANCE AND ADVERSE EFFECTS

Thiazide diuretics are underutilized likely because of concerns surrounding their adverse effects.[16]. However, low dose thiazide diuretics are well tolerated, as the symptomatic side effect profile is similar to that of placebo and other major drug classes (e.g. erectile dysfunction occurs in only 2% of men).[17,19] The asymptomatic side effects, including hypokalemia, renal dysfunction, dyslipidemia, and hyperglycemia although uncommon at low doses, need to be monitored. [18,19]

The development of hypokalemia among those using thiazide diuretics (although less frequent at low doses) is important since several observational studies have shown that hypokalemia in thiazide treated patients is associated with reduced cardiovascular benefit. In the ALLHAT study, only 8.5% of patients assigned to chlorthalidone develop hypokalemia. Serum potassium levels tend to fall, if at all, within the first two weeks of usage and rarely fall below 3.0 mmol/L for patients taking low doses.

Potassium levels should be monitored initially and hypokalemia should be treated with dietary modification or use of combination potassium sparing diuretics/thiazide diuretics (utilizing combination drugs such as hydrochlorothiazide/ amiloride, hydrochlorothiazide/ spironolactone, or hydrochlorothiazide/ triamterene). Potassium supplementation is less ideal since they are expensive and multiple tablets are often needed.

Rates of dyslipidemia, hyperglycemia and renal dysfunction are higher with thiazide diuretics,[15,19] but these disturbances are generally minimal, and dose dependent. Thiazide diuretics may precipitate gout however; high uric acid levels are not a contraindication to use.[17]

All patients starting on thiazide diuretics (even at low doses) should be initially screened for these metabolic parameters (glucose level, electrolytes, creatinine and total cholesterol). Any abnormalities should prompt closer follow up and correction. While there may be increases in the incidence of diabetes mellitus, dyslipidemia, renal impairment and hypokalemia, these abnormalities appear to be minimal and uncommon at low doses. However, most importantly, low dose thiazides are extremely well tolerated and have overwhelming evidence of their cardiovascular benefits.

Cost

Although no definitive economic analysis has been performed from a Canadian society perspective, the cost per pill for low dose thiazides is pennies a day. In particular, thiazides diuretics are considerably less expensive than the other first line therapies and have significant cost advantages in persons who have difficulty in affording their medication.

SUMMARY

Hypertension control remains one of the leading health priorities in Canada. There is strong high quality evidence favoring the use of low dose thiazide diuretics in the treatment of hypertension to reduce blood pressure and cardiovascular disease and death. Although the use of these drugs require monitoring of side effects, low dose thiazides are extremely well tolerated and should be increasingly used by primary care physicians as a first line therapy for treatment of hypertension.

TABLE 1 Recommended indications for use in hypertension

First Line Agent:
Diastolic ± systolic hypertension without compelling indications
Isolated systolic hypertension without compelling indications
Diabetes mellitus without nephropathy
Left ventricular hypertrophy
Past history of CVA/TIA (in combination with ACE inhibitor)
Second Line Agent:
Diabetes mellitus with nephropathy (additive to ACE inhibitor or angiotensin receptor blocking agents)
Heart failure (additive therapy to ACE inhibitor)
Renal disease (additive therapy to ACE inhibitor)

Adapted from table 2. (ref 3)

TABLE 2 Adverse effects associated with thiazide diuretic use

Hypokalemia (potassium <3.5 mmol/L)
Hyperglycemia
New onset of diabetes mellitus
Renal dysfunction
Hyponatremia
Dyslipidemia
May precipitate gout
Erectile dysfunction
Hypotension
Pregnancy risk: B (FDA Use –in Pregnancy Ratings for Drugs. B= no evidence of risk in humans)
Lactation: present in breast milk

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REFERENCES

1. Joffres MR, Hamet P, Rabkin SW, Gelskey D, Hogan K, Fodor G.Prevalence, control and awareness of high blood pressure among Canadian adults. Canadian Heart Health Surveys Research Group.CMAJ. 1992; 146 (11): 1997-2005.
2. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS.Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003; 289 (19): 2534-44.
3. Feldman RD for the Canadian Hypertension Education Program. What's new in the 2003 hypertension guidelines. Perspectives in Cardiology. 2003;19:44-51
4. Campbell NRC, McAlister F, Brant R, Levine M, Drouin D, Feldman R, Herman R, Zarnke

K for the Canadian Hypertension Education Process and Evaluation Committee. Temporal trends in antihypertensive drug prescriptions in Canada before and after introduction of the Canadian Hypertension Education Program. J Hypertens. (In Press)
5. Shah S, Khatri I, Freis ED. Mechanism of action of thiazides diuretics. Am Heart Journal 1978; 95:611-8
6. Pickkers P, Hughes AD, Russel FGM, Thien T, Smits P. Thiazide-induced vasodilation in humans is mediated by potassium channel activation. Hypertension 1998; 32:1071-6.
7. Shah S, Khatri I, Freis ED. Mechanism of action of thiazides diuretics. Am Heart Journal 1978; 95:611-8
8. Cushman WC, Khatri I, Materson BJ, Reda DJ, Freis ED, Goldstein G et al. Treatment of hypertension in the elderly. III response of isolated systolic hypertension to various doses of hydorchlorothiazide: Results of a Department of Veteran Affairs cooperative study. Arch Intern Med 1991; 151:1954-1960
9. Kaplan NM. The case of low dose diuretic therapy. Am J Hypertens 1991; 4:970-1
10. Frishman WH, Bryzinski BS, Coulson LR et al. A multifactorial trial design to assess combination therapy in hypertension: treatment with bisoprolol and hydrochlorothiazide. Arch Intern Med 1994; 154:1461-1468
11. Peters, DC, Noble S, Plosker GL. Trandolapril. An update of its pharmacology and therapeutic use in cardiovascular disorders. Drugs 1998; 56:871-888
12. Progress Collaborative Group. Randomized trial of a perindopril-based blood pressure-lowering regime among 6105 individuals with previous stroke or transient ischaemic attack. The Lancet 2001; 358:1033-1041.
13. Frishman WH, Bryzinski BS, Coulson LR et al. A multifactorial trial design to assess combination therapy in hypertension: treatment with bisoprolol and hydrochlorothiazide. Arch Intern Med 1994; 154:1461-1468
14. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA. 1997; 277(9): 739-45.
15. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288 (23): 2981-97
16. Moser M. Why are physicians not prescribing diuretics more frequently in the management of hypertension? JAMA. 1998; 279(22): 1813-6.
17. Neaton JD, Grimm RH, Jr., Prineas RJ, et al. Treatment of mild hypertension study. Final results. JAMA. 1993; 270:713-24
18. Cushman WC, Khatri I, Materson BJ, Reda DJ, Freis ED, Goldstein G et al. Treatment of hypertension in the elderly. III response of isolated systolic hypertension to various doses of hydorchlorothiazide: Results of a Department of Veteran Affairs cooperative study. Arch Intern Med 1991; 151: 1954-1960
19. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomized trials. BMJ 2003; 326: 1427-0.