DIURETICS IN THE TREATMENT OF HYPERTENSION: CURRENT STATUS

1. When are thiazide diuretics considered first line antihypertensives?

• Antihypertensive therapy should be individualized by choosing agents that have favorable effects on comorbid conditions.
• The recent **JNC VI** report[1] recommends thiazides (or β Blockers) as first line agents in the treatment of uncomplicated hypertension except where contraindicated, not tolerated, or concurrent medical conditions favor use of alternate agents (see Appendix 1).[1] Thiazide diuretics and β Blockers are the only antihypertensives that have been well documented in long-term controlled trials to reduce cardiovascular morbidity and mortality, particularly MI and stroke.[2] Current large-scale trials are underway to determine if other classes of antihypertensives have similar benefits. Thiazides are particularly effective in elderly patients with isolated systolic hypertension.[1] They also have favorable effects in patients at risk of osteoporosis. When not used for initial monotherapy, addition of a low dose diuretic as the second agent is recommended unless contraindicated.[1]

2. Are low dose thiazides as effective in treating hypertension as higher doses?

• Doses as low as **12.5-25mg** of hydrochlorothiazide (HCT), given once daily, have been as effective in lowering blood pressure as higher doses.[3] In fact, doses above 25mg have little added benefit but greater incidence of adverse effects.[3,7] A dose of 6.25mg HCT can often significantly augment the response of other antihypertensives when used in combination.

3. What about the adverse metabolic effects of thiazides?

• **In doses of 25mg or less**, incidence of hypokalemia is <5%, and few patients will actually require potassium supplementation or addition of a K+ sparing diuretic. Potassium levels should be checked within 1-2 weeks of therapy initiation. Incidence of hyperglycemia is increased with doses of >25mg. Generally, thiazides are not considered suitable for use in diabetics. Hyperuricemia occurs in <5% of patients and is usually asymptomatic unless there is a history of gout. Thiazides may cause modest changes in lipid profiles but these are often transient, returning to baseline values after 1 year; clinical significance is likely minimal as benefits appear to outweigh risks.[4] **Indapamide** does not affect lipids or glucose significantly.

4. How do thiazides compare to calcium antagonists, ACE inhibitors, and other antihypertensives?

• At comparable doses, all classes of antihypertensives have **similar efficacy** rates and are effective in ~50% of patients with mild to moderate hypertension.[5] Although effective in lowering blood pressure, the ability of ACE inhibitors and calcium channel blockers (CCBs) to prevent morbidity and mortality is not yet established. Several large comparative trials are currently underway. The safety of CCBs is under review due to possible risks of adverse cardiac events, cancer, and bleeding.[6]
• Most side effects seen with thiazides are dose-dependent and can be **minimized with low dose therapy**. At low doses antihypertensive efficacy is maintained while adverse effects are significantly reduced.[7] In recent clinical trials comparing both old and "new" antihypertensives, low dose diuretics were well tolerated, showing comparable quality of life (QOL) measures to other agents such as ACE inhibitors and calcium channel blockers.[8] In TOMHS, chlorthalidone and acebutolol actually had superior improvements in QOL scores compared to amlodipine, doxazocin, and enalapril.[9]

COMPARISON CHART: *Low Dose* Diuretics in Hypertension

Drug	Comments (response usually seen within 4 weeks)	Usual Low Dose (for hypertension)	$ Cost* 30 Days
Hydrochlorothiazide (HCT) (HydroDiurel®) 25mg,50mg tab	•low dose (**≤12.5mg**) effective with minimal side effects/metabolic effects. •half tab for 12.5mg dose; 6.25mg enough to augment other agents •scored •available low-dose in some combination products (Prinzide®/Zestoretic®, Hyzaar®)	12.5-25mg OD	8.00
Chlorthalidone (Hygroton®) 50mg,100mg tab	•disadvantage: low dosage requires quartering of tabs or EOD dosing •scored tablet	12.5-25mg OD (or 25mg EOD)	7.50
Indapamide (Lozide®) 1.25mg,2.5mg tab	•less effect on lipids & glucose metabolism. •may be preferred in patient with hyperlipidemia or diabetes •long-term efficacy data not yet available •high cost for a diuretic; but low cost for an antihypertensive	1.25-2.5mg OD	18.90
Combination Diuretic Products	(***Low Dose*** may require using ½ tablet or possibly every other day dosing)		
Dyazide®	•HCT(25mg) and triamterene(50mg) •K+ sparing •scored tablet	½ - 1 tab OD	8.70
Moduret®	•HCT(50mg) and amiloride(5mg) •K+ sparing •use ½ tab for low dose	½ tab EOD-OD	10.50
Aldactazide-25® (also –50)	•HCT(25mg) & spironolactone(25mg) •aldosterone antagonist; K+ sparing	1 tab EOD-OD	10.60

References: *cost = maximum retail cost to consumer & includes markup & dispensing fee (Saskatchewan)

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[3] Flack J and Cushman W. Evidence for the efficacy of low-dose diuretic monotherapy. Am J Med. 1996;101(supp 3A);53S-60S.
[4] Thiazide diuretic induced hyperlipidemia.(drug consult) Micromedex inc. Vol.95
[5] Fries E and Papademetriou V. Current drug treatment and treatment patterns with antihypertensive drugs. Drugs. 1996;52(1):1-16.
[6] Special review on the safety of calcium channel Blockers. April 1, 1997. Health Canada.
[7] Black H. The evolution of low-dose diuretic therapy; the lessons from clinical trials. Am J Med. 1996;101(supp 3A):47S-52S.

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[9] Grimm RH, Grandis GA, Cutler JA et al. Relationships of quality of life measures to long term lifestyle and drug treatment in the Treatment of Mild Hypertension Study. Arch Intern Med. 1997;157:638-48.