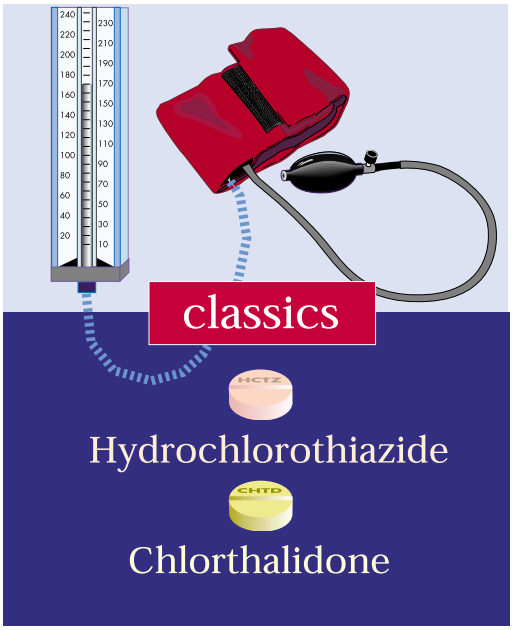
THERAPEUTICS INITIATIVE
Evidence Based Drug Therapy

Drugs of Choice in the Treatment of Hypertension

Part 1

We are bombarded with suggestions as to what should be our drug of first choice in the management of patients with documented elevated blood pressure. Is it appropriate to choose randomly from the wide array of available drugs, or is there a way to rationally pick the drug which is most likely to benefit our patients? By setting up a hierarchy of the issues which are most important, and compiling and critically appraising the presently available evidence, it is possible to narrow the choice to one or two drugs (see picture). The issues that are significant in descending order of importance include: evidence of effectiveness in decreasing the complications associated with hypertension, efficacy in lowering blood pressure, tolerability, convenience of dosing, and cost.



• What evidence do we have about the effectiveness of antihypertensive drugs in preventing cardiovascular diseases?

Studies to answer this question must be randomized, controlled, and double-blind to prevent bias and must be large and of sufficient duration. In 1990 a meta-analysis of the 14 trials which met defined criteria was published.[1] This analysis (mean age 52 years, 53% male), demonstrated that a 5-6 mm Hg decrease in diastolic blood pressure produced a 14% reduction in coronary heart disease, and a 42% reduction in cerebrovascular accidents over a 5 year follow-up period. Since 1990, five additional trials have been published. These trials have confirmed and strengthened the original meta-analysis, and demonstrated a greater relative and absolute risk reduction, particularly for coronary artery disease in the elderly[2] plus the benefit of treating isolated systolic hypertension.[3] Most of the patients in these trials received thiazide diuretics as the only drug or as a component of the treatment. We therefore have compelling evidence of the effectiveness of this class of drugs in reducing morbidity and mortality in patients of all ages and types of hypertension. Beta blockers have also been studied as a single agent, but have not consistently shown an equal benefit: in a trial comparing atenolol with hydrochlorothiazide/amiloride, both drugs lowered blood pressure to the same degree but only the thiazide was associated with a decreased risk of stroke and coronary events.[4] We therefore cannot assume that an equal reduction in blood pressure will be associated with an equal benefit. Other classes of antihypertensives have not been assessed in effectiveness trials.

• Are there differences in blood pressure lowering efficacy?

There are many trials comparing efficacy, but the most relevant trial is the TOMHS study.[5] In this study with an average 4.4 years of follow-up 5 antihypertensive drugs and placebo were compared in 902 patients with mild hypertension. The drugs and daily doses used were thiazide-like diuretic, (chlorthalidone, 15 mg), beta-blocker, (acebutolol, 400 mg), ACE inhibitor, (enalopril 5 mg), alpha$_1$-antagonist, (doxazosin, 2 mg), and calcium antagonist, (amlodipine, 5 mg). The blood pressure lowering efficacy of all the five drugs was similar and greater than placebo. For chlorthalidone, but not for the other drugs, left ventricular mass declined more than for participants given placebo.

• Are there differences in tolerability or quality of life measures?

In the same trial a significant improvement in quality-of-life indexes was seen with acebutolol and chlorthalidone but not with the other drugs. The incidence of impotence was greater in men assigned to placebo than those assigned to drug treatment.

• Are there differences in convenience or cost?

The preferred regimen for chronic preventive therapy is once daily dosing. All thiazide and thiazide-like drugs should be prescribed only once daily in the morning. There are significant cost differences. (see Table and next letter). Hydrochlorothiazide is the least expensive of all antihypertensive drugs available in B.C.

• What about the metabolic consequences of thiazide therapy?

Using recommended low-dose regimens (table) the incidence of hypokalemia is small (1% of patients in the SHEP study had K^+ below 3.2 meq/L).[3] In patients who develop hypokalemia a K^+-sparing diuretic should be added (see Table). Do not prescribe K^+ supplements; they are inconvenient and expensive. The small increase in total cholesterol (2.5%) and triglycerides seen in some studies was not seen in the TOMHS study[5] and has not been proven to have any adverse consequences. The hyperglycemic effect is also small and did not have any consequences in the SHEP study in which at least 10% of patients had NIDDM on entry.[3] Thiazides can be safely used for the treatment of hypertension in NIDDM, except in patients where significantly worsened glucose control has been proven. Elevations in uric acid seen with thiazides are innocuous; thiazides should not be used in patients who develop recurrent gout with thiazide therapy.

• What is the mechanism of antihypertensive action of thiazides?

Thiazides and indapamide have direct vasorelaxant effects on resistance vessels. The thiazides are acting on calcium activated potassium channels and indapamide is acting as a calcium antagonist.[6] Therefore indapamide cannot be used interchangeably with the thiazides. The diuretic action of these drugs may have only minor importance in the overall antihypertensive effect.

• Conclusion

Based on the evidence available at this time and using criteria of effectiveness and cost, thiazides are clearly the drug of first choice. Based on the criteria of efficacy, tolerability and convenience, thiazides are equivalent to or better than all other drugs. Therefore, thiazides are the drug of first choice for most uncomplicated hypertensive patients. There will be a proportion of patients (20-25%) where thiazides are proven ineffective or inappropriate. In these patients or in patients requiring more than one drug, other drugs must be substituted or added. These other drugs will be discussed in the next Therapeutics Letter.

Table: Dosing and Cost of Diuretics for the Treatment of Hypertension

Diuretic	Trade name	Usual Dosage Range	Daily Cost* (in cents)
Hydrochlorothiazide 25 mg	**Hydrodiuril®, generic**	**12.5 - 25 mg daily**	**0.3 - 0.6**
Chlorthalidone 50 mg	**Hygroton®, generic**	**12.5 - 25 mg daily**	**1.2 - 2.4**
Bendroflumethiazide 2.5 mg capsules	Naturetin®	1.25 - 2.5 mg daily	6.6 - 13.3
Indapamide 2.5 mg capsules	Lozide®	2.5 mg daily	55.5
Potassium sparing			
HCTZ (25mg)/triamterene (50 mg)	Dyazide®, generic	1/2 -1 tablet daily	2.5 - 5.0
HCTZ (50mg)/amiloride (5 mg)	Moduret®,generic	1/4 - 1/2 tablet daily	5.9 - 11.9
HCTZ (25mg)/spironolactone (25 mg)	Aldactazide®,generic	1/2 - 1 tablet daily	5.6 -11.2
Triamterene (50,100 mg)	Dyrenium®	25 - 50 mg daily	9.9 - 13.1
Amiloride (5mg)	Midamor®	2.5 - 5 mg daily	15.2 - 30.4
Spironolactone (25, 100 mg)	Aldactone®, generic	25 - 100 mg daily	8.8 - 27.6

*** Least expensive available formulation in B.C, 1993**

References

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The Therapeutics Initiative was established to disseminate up to date evidence based drug therapy information to physicians and pharmacists. We are also committed to evaluating the effectiveness of all our educational activities using the Pharmacare data base. The data will be in a form such that individual physicians, pharmacies or patients will not be identified. If you do not wish to be part of this evaluation process, please notify us and you will be excluded from the evaluation.

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