Diuretics in the Treatment of Hypertension

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Summary: Diuretics are powerful agents that impair sodium reabsorption in renal tubules. Their ability to alter long-term sodium balance induces important hemodynamic changes that result in a reduction in peripheral resistance and sustained reduction in blood pressure. A pharmacologically diverse group of drugs, they remain a mainstay in the therapy of hypertension. Clinical trials over the past 4 decades consistently have shown that blood pressure lowering obtained from a diuretic-based regimen reduces cardiovascular events. The ability of diuretics to augment the efficacy of nearly all other classes of antihypertensives makes them highly versatile and an important pharmacotherapeutic intervention to achieve blood pressure control. This article reviews key aspects of the use of diuretics relevant to the clinical management of hypertension.
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Reduction in sodium and extracellular fluid volume has long been recognized for its ability to reduce blood pressure.[1] Until the late 1950s, options for diuretic therapy to achieve successful natriuresis and sustain reductions in fluid volume were limited, and the reality of diuretics as effective antihypertensives remained elusive. The discovery of the first effective orally acting diuretic, chlorothiazide, signified the beginning of the modern era of diuretic therapy.[2,3]

More than half a century later, diuretics continue to occupy a prominent place in the pharmacotherapy of hypertension. Certain subgroups, such as African Americans and the elderly, tend to be more responsive to diuretics because of the prominent role of volume-related mechanisms,[4] although the pervasive consumption of dietary sodium in modern society ensures that a substantial proportion of patients in all subgroups will respond.

In this context, it is clear that the lack of appropriate diuretic use is often responsible for failure to control blood pressure,[5,6] and, in many patients, hypertension cannot be controlled without use of a diuretic.

THE ROLE OF THE THREE MAJOR TYPES OF DIURETICS IN TREATING HYPERTENSION

Three main classes of diuretics are used in managing hypertension: the thiazides (and thiazide-like drugs), the loop diuretics, and the potassium-sparing agents (Table 1). The absolute natriuretic effect of each diuretic is determined by its pharmacology, principally by its site of action and its pharmacokinetic parameters. Renal physiology and its response to disease, along with patient-specific characteristics, must be appreciated to arrive at the appropriate selection and dosing of the diuretic.

When a diuretic is indicated in the chronic management of hypertension, the thiazides and thiazide-like agents are preferred for several reasons. First, they are conveniently dosed once, or in some cases twice, daily. Although they work in the early part of the distal tubule where only 5% of sodium is reabsorbed, their longer plasma half-lives relative to other diuretic classes allow them to exceed the natriuretic threshold drug level for a period of time sufficient to permit convenient once- or twice-daily dosing.[7] The prolonged low-level diuresis induces important hemodynamic changes (Fig. 1) that culminate in the lowering of systemic resistance and sustains long-term lowering of blood pressure.[8] Although blood pressure lowering with diuretics most likely occurs through reduction in arterial resistance seen over several months, doses can be titrated approximately 2 to 4 weeks after initiation.

Second, thiazides are highly effective in lowering blood pressure. With conventional dosing as monotherapy, they lower systolic blood pressure 10 to 15 mm Hg compared with placebo. Third, thiazides are versatile in that they can be combined effectively with nearly any antihypertensive class to produce a blood pressure–lowering effect that is additive of the two individual components in most cases.[4]

Loop diuretics, which interfere with sodium reabsorption in the thick ascending limb, are shorter-acting than thiazides. Consequently, they are subject to a significant post-dose antinatriuretic period (ie, a braking effect) of several hours, a compensatory response designed to minimize further volume losses. This period of sodium reabsorption occurs in response to a decline in the drug

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Table 1. Diuretics Commonly Used in the Treatment of Hypertension

Diuretic Classification, Individual Agents	Site of Action, Maximum % of Filtered Sodium Load	Enzyme/Channel Inhibited	Usual Effective Dose Range, Hypertension*
Thiazide	Early distal convoluted tubule (5%-8%)	Na^+-Cl^- symporter	
Hydrochlorothiazide			12.5-50 mg/d
Bendroflumethiazide			5-20 mg/d
Thiazide-like			
Chlorthalidone			12.5-25 mg/d
Metolazone			0.5-5 mg/d
Indapamide			1.25-5 mg/d
Loop	Thick ascending limb of loop of Henle (20%-25%)	Na^+-K^+-$2Cl^-$ symporter	
Furosemide			20-200 mg once or twice daily
Torsemide			5-20 mg/d
Bumetanide			0.5-3 mg/d
Potassium-sparing	Cortical collecting duct (2%-3%)	Epithelial sodium channel (amiloride, triamterene)	
Amiloride			5-20 mg/d
Triamterene		Aldosterone receptor (spironolactone, eplerenone)	50-200 mg/d (monotherapy) 37.5-75 mg (in fixed-dose combinations)
Spironolactone			12.5-50 mg/d
Eplerenone			12.5-100 mg/d

*Usual dose range balancing antihypertensive efficacy and safety.

level to below the diuretic threshold,[4] and diminishes the efficacy of loop diuretics in lowering blood pressure. Loop diuretics are not usually used in hypertensive patients with normal renal function. They typically are used in patients with reduced renal function because of the large capacity for sodium reabsorption in the thick ascending limb. They also are used in patients needing a diuretic who have a history of an allergic reaction to a thiazide, or a history of thiazide-induced hyponatremia. When hypertension accompanies the presence of edematous disorders such as in renal disease, loop diuretics become the primary diuretic therapy.

Potassium-sparing diuretics are widely recognized for their ability to protect from potassium loss induced by thiazide and loop diuretics. By blocking the effects of aldosterone, mineralocorticoid antagonists such as spironolactone and eplerenone are also very effective in reducing blood pressure.[9] Potassium-sparing agents that do not have effects on mineralocorticoid receptors, and instead have direct effects in the distal tubule, including amiloride and triamterene, also protect from potassium loss, while lowering blood pressure.

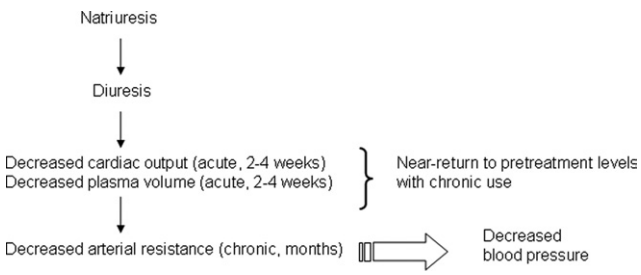

Figure 1. Physiologic effects of diuretics that lead to sustained lowering of blood pressure.

The potassium-sparing agents are widely used in combination with thiazide and loop diuretics. Such combinations provide an important alternative to increasing the dose of a thiazide diuretic that can enhance blood pressure lowering without the adverse metabolic effects of a higher dosage of a thiazide. In general, blood pressure lowering is modest with these agents, particularly triamterene, when used in the doses found in commercially available fixed-dose combinations. Potassium-sparing diuretics can be prescribed by themselves, without coadministration of a thiazide or loop diuretic, in patients with contraindications or intolerance to the latter. In black patients, amiloride was more effective in lowering blood pressure than spironolactone when added to existing therapy.[10]

DOSE-RESPONSE CONSIDERATIONS

An important evolution in the use of diuretics has been in their dosing. High dosages, such as 100 to 200 mg/d of hydrochlorothiazide, were once widely prescribed.[11-13] In more recent decades, lower doses such as 12.5 to 25 mg of hydrochlorothiazide or chlorthalidone, customarily have been prescribed.

A long-standing debate has centered on the dose-response characteristics of thiazide diuretics. A series of studies conducted in the 1970s helped elucidate this issue.[14-16] It is now appreciated that for most patients, the antihypertensive effect is achieved at a low dose. Approximately 50% of patients will respond to a low dose such as 12.5 mg/d of hydrochlorothiazide. Increasing the