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Thiazide-Type Diuretics: Ongoing Considerations on Mechanism of Action

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Thiazide-type diuretics have enjoyed a considerable success in the management of hypertension. These drugs have assumed a standard-of-care position in the minds of many health care providers; however, a number of questions remain unresolved in relation to their use. Such questions include issues of mechanism of action, comparability to loop-diuretics in their actions, class-effect, and the basis for their additivity with non-diuretic antihypertensive medication classes. Understanding these issues is important to the effective use of these compounds.
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Thiazide-type diuretics have been employed in the treatment of hypertension for nearly a half-century. Despite the considerable treatment experience with these compounds, a number of uncertainties remain concerning their use. Of the unanswered questions concerning thiazide-type diuretics, several are worthy of comment: 1) what is the mechanism of action of a thiazide-type diuretic and to what degree is a persistent reduction in extracellular fluid (ECF) volume a prerequisite for continuing blood pressure (BP) reduction with these compounds? 2) do thiazide-type diuretics provide BP reduction in excess of that seen with loop diuretics? 3) are all thiazide-type diuretics the same in their BP-reducing effect? and 4) with which drug classes do thiazide-type diuretics additively reduce BP?

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ECF VOLUME CHANGES WITH THIAZIDE-TYPE DIURETICS

The precise means by which a thiazide-type diuretic lowers BP is undecided. The effect of a thiazide diuretic on BP may be separated into three chronological phases: 1) acute; 2) subacute; and 3) chronic, which correspond to periods of roughly 1–2 weeks, several weeks, and several months, respectively.[1] In the acute response phase, the BP-lowering effect of a diuretic is coupled to a reduction in ECF volume and a related fall in cardiac output. The early response (first 2–4 days of treatment) to a thiazide-type diuretic, in the setting of a "no salt-added" diet (100–150 mmoL/d), results in a net sodium (Na^+) loss of from 100–300 mmoL, which amounts to a 1–2 L (or an approximate 12% decrease) in ECF volume.[2] There is a similar reduction in plasma volume with a thiazide diuretic, which indicates that this acute volume loss arises proportionally from both the plasma and interstitial compartments.[3] This decrease in plasma volume both reduces venous return and diminishes cardiac output, thereby the basis for the initial BP fall with a thiazide diuretic.[4]

This change in plasma volume with a diuretic can stimulate both the sympathetic nervous system and the renin-angiotensin-aldosterone system. The degree to which these systems activate governs

the magnitude of the acute BP decrease with both diuretic monotherapy and diuretics given in combination with agents that interrupt the renin-angiotensin-aldosterone system.[4] In due course, the effect of a thiazide-type diuretic on volume and cardiac output lessen in importance, although BP remains lowered. During the subacute phase of a treatment response (first few weeks), plasma volume returns to slightly less than pretreatment levels, despite the continued administration of a diuretic.[3] This subacute response phase is a transitional period during which both volume and resistance factors contribute to the BP reduction with thiazide-type diuretics.[4–5]

In the chronic response phase of therapy the vasodepressor influence of a diuretic emerges as a process driven by a reduction in total peripheral resistance (TPR), which is inadequately explained mechanistically. The decrease in TPR during prolonged diuretic therapy has been ascribed to several factors: including changes in the ionic content of vascular smooth-muscle cells, altered ion gradients across smooth-muscle cells and/or potassium-channel activation, changes in membrane-bound adenosine triphosphatase activity, and/or a process of autoregulation, which adjusts for the low cardiac output by vasodilation, and hence restores cardiac output to normal.

The ability of thiazide-type diuretics to reduce BP seems to be linked to the presence of functioning renal tissue; thus, these drugs will not reduce BP in hemodialysis patients.[6]

A mechanistic understanding of both diuretic action and the countervailing forces triggered by diuresis is needed for a well-reasoned approach to the treatment of hypertension. The early action of diuretics to reduce ECF volume is optimized if dietary Na^+ is limited at the start of therapy. This limits the repercussions of the braking phenomenon, which is a common occurrence with uninterrupted diuretic use.[7] Some limitation in dietary Na^+ intake may also be relevant to how diuretics chronically reduce TPR. It is thought that adjustments in Na^+/Ca^{2+} balance in vascular smooth muscle cells take place with the acute volume contraction seen during the first several days of thiazide diuretic therapy. How this phenomenon of volume contraction specifically translates into a reduction in TPR remains unclear.[1–2] Whatever the mechanism, it can be quite long-lived, because a residual BP reduction can be seen several weeks after the withdrawal of thiazide diuretics (even without interposing nonpharmacologic treatments for maintenance of BP control)[8–9]; however, this residual BP-reducing effect of thiazide-type diuretics has not been carefully compared with that observed with other antihypertensive medication drug classes.[9]

Another consideration in the chronic BP reduction with a diuretic relates to the duration of a natriuretic response. For example, when long-term responses to hydrochlorothiazide (HCTZ) and furosemide are compared in hypertensive patients, systolic and less so diastolic BP are more consistently reduced with HCTZ.[10–11] This difference has been attributed to the more gradual and prolonged diuresis with a thiazide diuretic (with a less profound braking phenomenon) compared with the brisk and early diuretic response with a loop diuretic (more significant braking phenomenon). In the end, during the acute phase of response a thiazide diuretic may be able to maintain a mild state of volume contraction more effectively than a loop diuretic.[7] It is thought that this pattern of volume removal with a thiazide-type diuretic lends itself to a greater downward shift in TPR. A direct vasodilator effect of HCTZ had been postulated but when studied is quite small and only occurs at high, local concentrations when infused into the human forearm.[12]

DIURETIC CLASS EFFECT

The concept of "class effect" has been applied to both loop diuretics and thiazide-type diuretics in respect to the management of hypertension. In this regard, loop diuretic effect on BP is a function of at least two processes: 1) the manner in which volume removal occurs; and 2) the ability of these compounds to independently decrease TPR. It has been observed that small doses of the long-acting loop diuretic torsemide may cause significant BP reduction in essential hypertensives, a process (one not demonstrable with sub-diuretic doses of furosemide) that seems to be independent of the observed degree of diuresis.[13] Of note, furosemide does not directly dilate human forearm arterial vessels even at supratherapeutic concentrations[14]; however, furosemide, given in bioequivalent doses to stage II–III chronic kidney disease patients, is equally effective as torsemide in reducing 24-hour ambulatory BP.[15] Until comparison studies amongst loop diuretics are carried out in diverse populations, it is premature to presume that loop diuretics are distinguishable (independent of volume removal) in their BP-reducing ability.

The idea of class effect for thiazide-type diuretics is one promulgated by many, but with minimal experimental support.[16] Much of the recent debate on thiazide-type diuretic-class effect has focused

on the similarities (or not) between chlorthalidone and HCTZ.[17] The concept of class effect with thiazide-type diuretics needs to be considered in two ways: 1) BP fall; and 2) event-rate reduction. These two compounds are fundamentally different diuretics in that chlorthalidone has a considerably longer duration of diuretic action than HCTZ; however, this does not imply that chlorthalidone is a superior antihypertensive compound. It is likely, though, that the longer duration of diuretic action with chlorthalidone makes it a milligram-to-milligram stronger antihypertensive compound than HCTZ. The exact dose equivalence between these two compounds is a matter of some debate and one that will not be easily resolved. As to the issues of outcomes, chlorthalidone has had a more consistent pattern of favorable outcomes than is the case with HCTZ.[17–20] Although it is tempting to assume that chlorthalidone is a better outcomes drug than HCTZ, until this has been prospectively studied, this can only be viewed as an assumption.

ADDITIVITY WITH NONDIABETIC ANTIHYPERTENSIVE DRUG CLASSES

BP can be readily controlled by a carefully selected prescription of two drugs without the necessity for high doses of either drug. For example, drug classes, which interfere with sympathetic nervous system activity (e.g., clonidine or a β blocker) may incite salt and water retention with the ensuing plasma volume expansion, returning BP values toward pretreatment values. Under these circumstances, BP control may be restored by the addition of a diuretic. In turn, patients having been successfully treated with diuretics can occasionally see BP control lapse because of the tendency for diuretics to activate the renin-angiotensin-aldosterone system and/or the sympathetic nervous system. Excess activity in these systems can be effectively reduced by adding a compound, such as an angiotensin-converting enzyme inhibitor, a β blocker, or an angiotensin receptor blocker, which reduces activity in the renin-angiotensin-aldosterone axis and helps to reestablish BP control. Finally, the repercussions from nonspecific vasodilator therapy (e.g., hydralazine or minoxidil) include salt-and-water retention, tachycardia, and variable activation of the renin-angiotensin-aldosterone axis. These are maladaptive responses, which are effectively fended off by combination therapy with diuretics and β blockers.[21]

It has been suggested that thiazide-type diuretic therapy has an additive effect on BP reduction with all drug classes other than calcium channel blockers (CCBs).[22–23] It was believed that the natriuretic effect of CCB therapy effectively replaced that of a thiazide-type diuretic; thus, if both drug classes were to be given together, the volume/vasodilator axis would be redundantly interrupted.[24] This has not proven to be the case and a significant number of trials have shown that thiazide-type diuretic therapy is additive with verapamil,[25–27] diltiazem,[28–30] and dihydropyridine CCBs.[31–32]

In assessing the additivity of a thiazide-type diuretic with a CCB, it should be appreciated that a sequence effect may exist. When a CCB is added to a diuretic, there is a potentiation of the antihypertensive effect.[26–27,33] When the order of administration is reversed, potentiation is less so.[22,26] This observation suggests that the BP-lowering effect of long-term thiazide-type diuretic therapy can be reenforced by the natriuretic and vasodilator actions of a CCB.[24,34] Alternatively, this sequence effect may simply reflect the lesser BP reduction seen with a diuretic, allowing a greater relative reduction to occur with a comparably more potent CCB.[35]

CONCLUSIONS

Diuretic therapy remains a vital cog in the management of hypertension; either as monotherapy or in combination with other antihypertensive classes. However, maximizing the antihypertensive effect of a diuretic is as much an art as it is a science. Of the questions concerning diuretic therapy: class effect, mechanism of action, and additivity with other medication classes are noteworthy issues. The manner in which thiazide-type diuretics reduce BP in the long term does not involve a "daily" diuresis. An appreciation of this is important since "diuresis" is an important tool in resistant hypertensives, even for those receiving a thiazide-type diuretic.

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