Attention must be paid to the article by Roush et al in this edition of Hypertension. The authors use robust statistics to compare the antihypertensive potency and adverse effects of hydrochlorothiazide versus indapamide in the 10 publications that could be identified, wherein the 2 drugs were compared head-to-head in trials lasting 24 weeks. Indapamide, used as 2.5 mg tablets in all but 1 trial, provided a 54% greater reduction in systolic blood pressure, that is, −5.1 mm Hg (confidence interval, −8.7 to −1.6) than seen with hydrochlorothiazide in doses from 12.5 to 50 mg/d. The relative doses were greater for hydrochlorothiazide in 5 trials and equivalent in 3 trials.

The blood pressures were measured by office sphygmomanometry in all these trials but reference is given to studies using 24-hour ambulatory measurements, which showed ≥24-hour duration of diuretic and antihypertensive efficacy with the immediate formulation of indapamide and ≥32-hour duration with the sustained formulation (which was used in only one of the trials). Roush et al refer to multiple additional vasodilatory actions described in the literature in support of the greater reduction of blood pressure and the longer duration of action of indapamide, well beyond the 12- to 16-hour duration of action of hydrochlorothiazide.

Indapamide Versus Chlorthalidone

The first 2 authors of this article have been involved in studies documenting a longer and stronger antihypertensive effect of chlorthalidone over hydrochlorothiazide, studies that were published as far back as 2004 and reiterated in the current article with data from 3 head-to-head comparisons.

No such comparisons between chlorthalidone and indapamide could be found. Both probably provide full 24-hour antihypertensive efficacy so the choice between them must be based on known additional characteristics of the 2 drugs. There are at ≥3 features which could influence the choice and all 3 favor indapamide over chlorthalidone. These are (1) Ease of use: In the US, generic chlorthalidone is only available as a 25 mg tablet. To approximate the most frequently used 12.5 mg dose of hydrochlorothiazide, the chlorthalidone tablet must be cut in half. Generic indapamide, both in the immediate and delayed action formulations, is available as 1.5, 2.5, and 5 mg tablets so no such manipulation is needed. (2) Cost: The cost of many drugs is higher in United States than in other countries, adding to the markedly higher spending on healthcare in the United States than in countries with a national healthcare system. The cost of 30 tablets of generic chlorthalidone in 4 local multiple-chain pharmacies varies from $21 to $31, whereas the cost of 30 tablets of all strengths of generic indapamide is $4.00. Most generic formulations of other classes of antihypertensive drugs are also available for $4.00 for 30 tablets. (3) Hypokalemia: The fall in serum potassium with 12.5 mg doses of chlorthalidone is ≈0.1 mmol/L greater than that seen with equivalent doses of hydrochlorothiazide. As noted by Roush et al, the fall in serum potassium with 2.5 mg/d doses of indapamide averages only 0.054 mmol/L more than that seen with hydrochlorothiazide.

In addition, no significantly greater changes in serum sodium, glucose, cholesterol, or uric acid were seen. The one advantage of hydrochlorothiazide over both chlorthalidone and indapamide is its extensive availability in formulations with other classes of antihypertensive drugs in both 12.5 and 25 mg doses, most of which cost only $4.00 for 30 tablets. Chlorthalidone is marketed only with the generally discredited β-blocker atenolol and the recently approved angiotensin receptor blocker azilsartan, but the cost of 30 tablets of this still patented angiotensin receptor blocker is $170.99. The only marketed combination of indapamide is with the angiotensin-converting enzyme inhibitor perindopril but this combination is not available in the 4 pharmacies contacted in Dallas.

Therefore, if a second drug is needed with indapamide, the cost of almost any of the generic formulations of the other classes of drugs should be only an additional $4.00.

Nocturnal Protection

The wisdom of using indapamide or chlorthalidone is supported further by Roush et al who wrote: “While HCTZ has less than a 24 hour duration of diuretic and antihypertensive actions, indapamide even in the immediate release form has at least a 24 hour duration of action for blood pressure reduction…. Duration of action is important in view of the fact that targeting nighttime BP may reduce cardiovascular events above and beyond the reduction in events relative to targeting daytime BP”.

The authors conclude that these head-to-head comparisons demonstrate that, like chlorthalidone, indapamide has a greater antihypertensive potency than hydrochlorothiazide at commonly prescribed doses without evidence for greater adverse metabolic effects.
The Addition of a Mineralocorticoid Receptor Antagonist

Although not addressed by Roush et al., one additional drug should be considered with whatever diuretic is chosen, namely a mineralocorticoid receptor antagonist (MRA). As most vigorously advocated by John Funder, an MRA will almost certainly provide additional cardiovascular protection to whatever type of antihypertensive drug used. In a recent review, he concludes that an MRA should be included in current antihypertensive therapy for all hypertensives with reasonable renal function and normal potassium levels.

The MRA spironolactone is available for $4.00 for 30 tablets but, inexcusably beyond financial avarice, the now generic and less bothersome MRA eplerenone remains costly in the United States, $114 for 30 tablets.

It may be even more difficult to convince practitioners to switch from hydrochlorothiazide to indapamide or chlorthalidone than to convince them to also add an MRA. If a choice is needed, the switch to indapamide seems most critical, at least until a generic formulation of indapamide combined with an MRA enters the therapeutic armamentarium, thereby most effectively controlling our most common and fastest growing cardiovascular risk factor.

Disclosures

None.

References
