Peterzan et al have provided an important new meta-analysis of the dose-response relationships for 2 different thiazide diuretics and 1 thiazide-like diuretic. The focus was on antihypertensive efficacy, with brief reference to alterations in serum electrolyte measures. More balance is required for proper clinical perspective.

The uniqueness of the study is the dose-stratified meta-analysis of the 3 most commonly used diuretics for antihypertensive treatment. The authors were strict in their inclusion criteria, limiting their analysis to only double-blind, placebo-controlled, parallel design trials in people with blood pressure \( \geq 160/90 \) mm Hg with treatment for \( \geq 4 \) weeks. Despite the limitations that they note in their article, including the use of older data where blood pressure measurement techniques and formulation differences may exist, fewer trials with chlorothalidone and bendroflumethiazide compared with hydrochlorothiazide lack of data examining the lower parts of the dose-response, the meta-analysis provides a novel observation indicating that the equivalent systolic antihypertensive effect of hydrochlorothiazide 25.0 mg is 8.0 mg with chlorothalidone and 1.5 mg with bendroflumethiazide. Interestingly, these antihypertensive effects are in line with the drug affinity for the NaCl cotransporter in the distal convoluted tubule. However, this meta-analysis did not evaluate the potency of diuretic effects between these drugs. It is likely that the antihypertensive potency may parallel the diuretic effects.

However, one has to balance the novel description of antihypertensive potency from this meta-analysis, with the observations of changes in serum potassium and uric acid. There was a clear dose-dependent effect of all 3 diuretics in reducing serum potassium and increasing serum uric acid. In fact, the slope of changes was similar for all 3 of the drugs. The authors proposed to look at serum glucose, cholesterol, and sodium, in addition to the serum potassium and uric acid. However, only the latter electrolytes were described in the article. We are not sure why these data were not reported, but one would surmise that similar dose-related changes likely occurred. This may be particularly important for serum glucose, where there is an established link between diuretic-induced hypokalemia and glucose intolerance. As with all therapies, one must balance the benefits versus risks. Blood pressure reduction is important, but alterations in metabolism may potentially offset some of the benefit of blood pressure reduction. Thus, a more important question than antihypertensive potency is the net change in serum potassium, glucose, uric acid, and so forth for a given 10-mm Hg change in systolic blood pressure with each of the diuretics.

Individualization rather than generalization is needed when choosing antihypertensive medications and doses. It is quite clear from this dose-stratified meta-analysis that not all thiazides and thiazide-like diuretics are alike in antihypertensive potency. If anything, there are substantial differences, which need to be considered when choosing these drugs.

However, there is no demonstrated difference in efficacy as long as one is using therapeutic equivalent doses. Diuretics, like all antihypertensive drugs, have a dose- clinical response curve. Another important consideration is that monotherapies are often not successful in controlling blood pressure in many patients. Thus, it is not a question of which “best diuretic” is the best to use but which diuretic and dose works well to lower blood pressure when combined with another antihypertensive agent in a given patient. The traditional pairing of 12.5 to 25.0 mg of hydrochlorothiazide with either a \( \beta \)-blocker or an inhibitor of the renin-angiotensin system is a proven effective antihypertensive strategy. However, it is clear that higher doses of hydrochlorothiazide may be required if more blood pressure reduction is needed, whether used alone or with another drug, or one should consider a switch to a more potent diuretic.

It is widely believed that doses of hydrochlorothiazide \( >25 \) mg are ineffective. This meta-analysis suggests otherwise. Although adverse effects are increased with higher doses, one also achieves a greater antihypertensive response. There is also significant heterogeneity of the antihypertensive response, especially in those patients who consume more salt or have chronic kidney disease; so individualization of drug dose to maximize therapeutic effect and minimize adverse effect is essential. It is also important to note that, given the heterogeneity of the blood response, it is difficult in an individual prospective trial to establish a dose-response cure, let alone combining data from multiple trials with many different types of patients, trial designs, and so forth. The authors should be congratulated for this important contribu-
tion to the literature on this topic. But, these results should not be misconstrued as an endorsement for using chlorthalidone or bendroflumethiazide as preferred diuretics for people with hypertension.

**Disclosures**

None.

**References**


Thiazide and Thiazide-Like Diuretics: Perspectives on Individualization of Drug and Dose Based on Therapeutic Index
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