Tip 27 (February 2017)

Metabolic benefits of thiazide diuretics (kidney stones and osteoporotic fractures )

Thiazide diuretics remain an important part of the antihypertensive armamentarium , although, because of potential adverse metabolic effects (dysglycaemia, dyslipidaemia, hyperuricaemia and gout, hypokalaemia and hyponatraemia) they are often now relegated to second or third place in the choice of antihypertensive agent - after RAS- blockers (ACE-inhibitor or ARB) and DHP calcium channel blockers (principally amlodipine). The British guidelines suggest a calcium channel blocker as first choice in individuals > 55 years of age and a RAS blocker for individuals < 55 years of age. Most individuals with hypertension require > 1 drug to get to target and the most popular combination is now RAS-blocker + DHP calcium channel blocker (principally amlodipine) - this is based in part on the results of the ACCOMPLISH trial(1) which showed improved cardiovascular outcomes for individuals with St 2 hypertension treated with an ACE-inhibitor - CCB combination, compared with those treated with an an ACE-inhibitor - thiazide combination, despite equivalent blood pressure-lowering in both arms.

Having said that, many people can't tolerate CCB's due to vasodilatory side-effects, in which case thiazides are the most reliable and effective alternative, either as monotherapy, or in combination with a RAS-blocker. In addition, few individuals with more severe forms of hypertension can be successfully managed without a thiazide diuretic, and in general, the most effective strategy in individuals whose blood pressure is not controlled on an optimal-dose combination of RAS-blocker and CCB is to add a thiazide diuretic.

But are there situations, in the management of hypertension, where thiazides should be used preferentially as the first choice of antihypertensive drug class? The answer is, yes, probably, and this relates to the effects of thiazides on calcium metabolism. These drugs significantly increase renal tubular calcium absorption (by contrast, loop diuretics like frisemide cause net renal calcium loss). This property has been used therapeutically for many years in the management of individuals with recurrent calcium-based kidney stones and hypercalciuria - by reducing urinary calcium concentration they reduce the risk of calcium stone formation(2).

The other situation where this property may be useful is in the prevention of osteoporotic fractures;- decrease in urinary calcium excretion may translate in to a possible benefit on bone mineral density. The ALLHAT Trial (3) first published in 2002 remains the largest antihypertensive drug trial ever conducted involving about 45 000 participants. High risk hypertensive patiest were randomised to receive treatment with regimens based on a thiazide (chlorthalidone), and ACE-inhibitor (lisinopril) and a calcium channel blocker (amlodipine). There was no difference in the primary outcome (a composite of cardiovascular events and death) between the 3 arms although in a secondary outcome (heart failure) chlorthalidone was superior to lisinopril and amlodipine. A post-hoc analysis of the ALLHAT trial has recently been published, looking at hip fracture rates(4). At approximately five years, those randomly assigned chlorthalidone had significantly fewer hip or pelvic fractures as compared with those assigned to either lisinopril or amlodipine. The authors concluded " if monotherapy is appropriate in a patient with hypertension and osteoporosis, thiazide-like diuretics may have advantages over ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers".

Take home message: Consider a thiazide diuretic as a first choice antihypertensive drug in patients with a history of calcium-based kidney stones, or with osteoporosis.

1. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. Jamerson K et al.N Engl J Med 2008; 359:2417-2428December 4, 2008DOI: 10.1056/NEJMoa0806182

2.Fink HA, Wilt TJ, Eidman KE, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med 2013; 158:535.

3.Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs. Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981-97.

4. Association of 3 Different Antihypertensive Medications With Hip and Pelvic Fracture Risk in Older Adults: Secondary Analysis of a Randomized Clinical Trial. Putnam R et al. JAMA Intern Med. 2017;177(1):67