CLINIC-IQ

Are Thiazide Diuretics an Effective Treatment for Hypertension in Patients With Chronic Kidney Disease?

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Question: Are thiazide diuretics an effective treatment for hypertension in patients with chronic kidney disease (CKD)?
Answer: Probably
Date answer was determined: December 19, 2006
Level of evidence for the answer: B. Post hoc analysis of a large double-blinded RCT and a single, small, double-blind, randomized crossover trial.
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Summary of the issues:

Thiazide diuretics have as their major site of action the thiazide sensitive Na^+/Cl^-cotransporter located in the early distal tubule of the kidney. By blocking approximately 40% of NaCl reabsorption at that site these drugs increase fractional excretion of sodium and provide a natriuresis with subsequent blood pressure reduction. Additionally, thiazides have been shown to have a second site of action on the blood vessel walls themselves.[1] Here the mechanism is by action on Cat-activated K^+ channels with subsequent vasorelaxation.

The drop in GFR associated with CKD has long been postulated to render thiazide action ineffective as there is increased proximal Na^+ reabsorption and a subsequent drop in sodium delivery to the distal tubule. With decreased Na^+ delivery to the distal tubule there is reduced potential Na^+ reabsorption by the Na^+/Cl^- cotransporter and hence reduced window of potential action by thiazide diuretics. As such, current recommendations favor using loop diuretics in the later stages of CKD as their mechanism of action is located earlier in the Loop of Henle prior to such extensive Na^+ reabsorption. However, the effect of thiazides on blood vessel walls may be unaffected by reductions in GFR, and so these agents may still be effective as anti-hypertensive agents even though they are no longer effective as diuretics.

Summary of the evidence:

There has only been one large trial to compare the use of diuretics with other antihypertensive agents in patients with CKD.[2] This was actually a post hoc analysis of The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The initial trial was designed to compare the cardiovascular outcomes of different antihypertensive agents in high-risk hypertensive patients.[3] The post hoc study then analyzed the data from (ALLHAT) to determine the comparative effectiveness of a calcium channel blocker, an ACE inhibitor, and a thiazide diuretic on reducing the incidence of renal disease outcomes in hypertensive patients with reduced GFR. The results demonstrated no difference in the rates of development of ESRD or worsening GFR between patient subgroups treated with a thiazide diuretic and those treated with either of the other two agents. Blood pressure control was also found to be equivalent in the three groups.

There have been no large studies of the effectiveness of thiazide diuretics on blood pressure control in patients with advanced CKD (stages 4-5), and most authors have assumed them to be ineffective versus loop diuretics based upon diminished diuretic effects.[4] There was a single randomized, crossover trial of seven patients with severe CKD and HTN which showed HCTZ to be superior to furosemide in increasing fractional excretion of sodium and equivalent in reducing blood pressure.[5] This trial was too small to warrant any change of practice alone; however, it does call to light the paucity of clinical evidence to support current practice guidelines. Further evidence is needed involving larger groups of patients to fully determine the place of thiazide diuretics in patients with advanced CKD.

Comments

The National Kidney Foundation Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease recommend treating hypertension in patients with CKD with combination therapy to include a diuretic.[4] They recommend the use of thiazide diuretics in CKD stages 1-3 and loop diuretics in stages 4-5. These recommendations were last updated in 2004.

Search terms: thiazide diuretics, chronic kidney disease, hyper-tension, and renal failure

Inclusion/Exclusion criteria

Studies that involved the use of thiazide diuretics in various degrees of renal failure; excluded studies that only included thiazide diuretics as part of a combination medicine without studying the

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effects of these agents independently.

List of articles reviewed

1. Calder JA, Schachter M, Sever PS. Direct vascular actions of hydrochlorothiazide and indapamide in isolated small vessels. *European J of Pharmacology* 1992; 220(1):19-26.
2. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT, Jr., Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs. a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2005 Apr 25; 165(8):936-46
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(23):2981-2997.
4. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004 May;43(5 Suppl 1):S1-290.
5. Knauf H, Mutschler E. Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure. *J Cardiovasc Pharmacol* 1995;26(3):394-400.