Should we give up hydrochlorothiazide as the diuretic of choice in hypertension?

Introduction to the controversy

RAC Editing Committee

Consensus on hypertension propose thiazides as the first order drugs for its treatment. In practice, hydrochlorothiazide is the most common thiazide for antihypertension, 97% of the prescriptions include diuretics as individual or combined agents. In recent years, the detailed analysis of the published information showed that the greatest benefits from thiazides in clinical trials had been achieved with chlorthalidone and indapamide, whereas there were fewer evidences of the clinical benefit and potency of hydrochlorothiazide in usual doses. These revisions have raised the debate about the need to replace hydrochlorothiazide, with preference to other agents. In the last European Congress of Cardiology, Frank Messerli –as agonist– and Susane Oparyl –as defender of hydrochlorothiazide– participated in this controversy. The RAC (Argentine Journal of Cardiology) Editing Committee tried to bring this controversy to the local level, but it could not be settled. The reason was unexpected: Despite having asked a high number of specialists in hypertension, we were unable to find someone to defend the hydrochlorothiazide.

Still, we have decided to publish the agonist's arguments, with the intention of leaving open the possibility for readers to send a refutation to his arguments.

It still causes concern that the diuretic of choice in practice is indefensible in theory.

Agonist

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The answer to this question could be considered as too normative, but a comparison between hydrochlorothiazide (HCTZ) and other diuretics available –particularly chlorthalidone (CT) and indapamide– would let us approach what would be the best choice of a diuretic for a scheme of antihypertensive treatment. Thiazide-related drugs are among the most commonly drugs used to treat hypertension; antihypertensive action and benefits to risk reduction for several final indicators have been widely documented (1) and should be included in all the schemes prior to considering refractory a patient who does not meet the therapeutic goals. Although there are several drugs in the group, the most commonly used –and almost exclusively in our environment– in clinical trials are HCTZ and CT; more recently, IP was introduced, and although it is classified as akin to this group, some of its characteristics are different.

PHARMACOLOGICAL PROPERTIES OF THE FAMILY OF THIAZIDES

HCTZ and CT share the site and the mechanism of action, while IP would have additional effects on vessels and on other segments of the renal tubule. HCTZ has a half life of 2.5 ± 0.2 hours, which gives a duration of action of 18 hours, while CT has a half life of 47 ± 22 hours and a duration of action over 72 hours; these figures vary in the literature. (2, 3) In patients with normal renal function, duration of action of HCTZ is approximately 18 hours and, as with other diuretics whose duration of action is < 24 hours and are administered in once-daily dosing, Na+ could be retained during the period with no pharmacological action. (4) In addition, the potency of CT is 1.5 to 2 times greater; this could be related in part to the increased volume of distribution based on its high concentration of red blood cells. (5) These pharmacokinetic properties will determine the greater potency through an accummulation of the drug, usually administered at intervals shorter than its half life; therefore, effects are more evident when compared to repeated doses with cumulative effect until the administration-elimination balance is reached, usually with the fifth dose. The effect of both drugs would be similar with single doses. The longer duration of action is relevant in the treatment of hypertension, since the desired drugs are those which maintain their therapeutic effectiveness with a once-daily dosing, and so is the protection conferred to BP maintainence in case of missing a dose.

Greatest potency should be considered when comparing both the therapeutic and adverse effects,

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since both result from the same mechanism of action. The increased offer of Na+ to the distal tubule favors the interchange to K+ and the resulting hypokalemia.

The IP has a half life of 14-18 hours and a duration of action ≤ 36 hours. There is an extended-release form that increases these parameters and produces similar effects with a lower total dose. (3)

Thiazides act from the tubular lumen by inhibiting Na+-Cl- symport at the beginning of the distal convoluted tubule. The effect of diuretics may be divided into three phases: The first phase, with increased Na+ excretion, and volume contraction with gradual decrease in PA; the second one is characterized by increased peripheral resistance and reduced minute volume, which return to the previous values in the third phase, in which decreased PA is also maintained, with discrete volume contraction and Na+ balance lower than the initial one, although it does not increase with continuous treatment. It is possible to maintain the low level of Na+ by avoiding the alternation of loss and gain when the Na+-Cl- symport inhibition is continuous, as in the case of CT, and not intermittent, as with HCTZ. (6)

Decreased glomerular filtration rate (GFR) slows the arrival of the drug to this segment, which prolongs half life and duration of action. This segment does not interfere significantly with the reabsortion of Na+ in patients with severely reduced glomerular filtration, while blood volume contraction may be a risk for patients with GFR < 40 ml/min (creatinine between 1.8 and 2.5 mg/dl), therefore its use is discouraged. There are no publications about the evaluation of half life and duration of action in different levels of GFR.

As regards IP, studies with ambulatory blood pressure monitoring (AMBP) described a lower increase of uric acid level and a higher reduction of microalbuminuria, the chances of using it with lower GFR, and a proper peak/valley relationship. (7, 8)

HYPOKALEMIA

Several adverse effects have been associated with thiazides; hypokalemia is the most feared of all because of the chances of cardiac events, from arrhythmias to fatal events. Lower insulin sensitivity and possibly the higher rate of incident diabetes would also be associated with hypokalemia. The drop in potassium levels with HCTZ is estimated in 0 to 0.7 mEq/L, while with CT it is about 0.2 to 0.7 mEq/L. (2) However, comparison is difficult, because results come from studies based on different methodologies. The magnitude of hypokalemia is associated with the dose (9) and the diet of each patient. Doses were much higher in the intial clinical trials –up to 200 mg/day–, in times in which the vademecum on antihypertensives was very limited and drugs caused adverse reactions more frequently, with poor patient tolerance. In more recent trials, it was determined that the use of appropriate doses provide more benefits in preventing events than the risk associated with hypokalemia or other metabolic disorders. (2, 6) A significant reduction in potassium levels with low doses of thiazides suggests the need to evaluate an alternative disorder of potassium management, such as hyperaldosteronism.

The SHEP study reported that, at one year, 7.2% of the patients in the CT group and 1% in the placebo group had K+ < 3,5 mEq/L; these patients had a higher risk of ictus and cardiac events than those with normal potassium levels. However, CT was associated with reduced relative risk of non-fatal myocardial infarction and coronary mortality, even when there were baseline electrocardiographic abnormalities. (10)

In the MRFIT study, the results that assigned CT a higher risk of secondary cardiovascular events at hypokalemia compared to HCTZ were wrongly interpreted, since CT was associated with lower levels of K+ and also with reduced mortality. Therefore, a preference for the choice of drug was not justified on this basis. (6)

RESULTS IN BLOOD PRESSURE

The first published comparative study evaluated HCTZ 100 mg/day with CT 50 mg/day and placebo in patients with diastolic BP ≥ 95 mm Hg. CT caused a higher reduction of blood pressure (25.1/10.1 mm Hg) and lower reduction of K+ (0.24 mEq/L) compared to HCTZ (18.1/8,0 mm Hg and 0.47 mEq/L respectively); both drugs showed reduction of BP and K+ compared to placebo. (11) Another study compared CT (50 mg/day) with two dose levels of the HCTZ + triamterene combination (25 + 50 mg/day, and 50 + 100 mg/day); the hypotensive efficacy of CT was greater than that of the combination, and was significant compared with the lowest level but not with the highest level. As expected, hypokalemia was present in the CT group, but not in those who received triamterene. (12)

A study of replacement of HTCZ by CT at the same dose (12.5 mg to 25 mg) in patients who did not meet the BP goals showed a significant reduction ($p = 0.035$) of systolic blood pressure, from 152 mm Hg (CI 95% 150-168 mm Hg) to 145 mm Hg (CI 95% 138-149 mm Hg), with no significant change in potassium levels. (13)

Four other studies, with different designs and doses that are now considered high, compared CT with HCTZ; results were consistent in favor of CT with respect to HCTZ alone or in combination. (14)

In a randomized, simple blind study with parallel groups, which included 30 patients with no previous antihypertensive therapy, and used low doses, HCTZ 25-50 mg/day versus CT 12.5-25 mg/day, even considering the equivalence 2:1 of the doses, CT caused a significantly higher reduction of systolic BP demonstrated with AMBP (–12.4 ± 1.8 mm Hg versus –7.4 ± 1.7 mm Hg; $p < 0.054$) both in the daily and the night averages (–13.5 ± 1.9 mm Hg versus –6.4 ± 1.8 mm Hg; $p < 0.009$); unfortunately, the peak/valley relationship was not determined. Systolic BP

levels were lower but not significant in ambulatory monitorings (–17.1 ± 3.7 mm Hg versus –10.8 ± 3.5 mm Hg; p = 0.84), and potassium variations were similar. The difference in night-time values coincides with longer half life, and is associated with an improved profile for cardiovascular prevention. (15)

RESULTS IN CARDIOVASCULAR INDICATORS AND EVENT PREVENTION

At the beginning of the MRFIT study, patients were assigned to CT or HCTZ at doses between 50 and 100 mg/d. It was the only comparative study with a long-enough follow-up to observe events. Seven years later, its Advisory Committee recommended that all patients received the highest dose of CT (50 mg), because mortality was significantly lower for this arm. (16) Compared with patients assigned to HCTZ, those who received CT showed a lower rate of non-fatal events (p = 0.0084), coinciding with lower systolic BP (p = 0.0067). (15) The trend towards a higher rate of events in the HCTZ group was reversed by switching to CT. CT (12.5-25 mg/day) was the baseline drug in the SHEP study, which was the first to demonstrate a significant reduction in the rate of ictus in elderly population with isolated systolic BP. (10)

A recent review points out that while both drugs have been shown to reduce the risk in clinical trials, major studies with CT, like HDFP, MRFIT, SHEP, and ALLHAT, have shown the reduction of cardiovascular events more firmly than the studies with HCTZ. (5) Although clinical trials with indapamide for the prevention of events have been carried out, there have been no comparative studies with other diuretics.

There is stronger evidence in cardiovascular events with the use of CT. (6) The SHEP study evaluated the effects of 12.5-25 mg of CT compared with placebo in 4,736 patients with hypertension; the rate of ictus was significantly lower, and a (non-significant) reduction of several fatal and non-fatal cardiovascular events was also observed. (10) The ALLHAT trial (17) consolidated CT as the first-step antihypertensive therapy, by demonstrating benefit due to reduction of incident heart failure. Beneficial effects were also observed in the HDFP study. (5)

IP demonstrated prevention of cardiovascular events in subjects over 80 years of age in the HYVET study, and in a combination with ACE inhibitors, for prevention of primary and secondary ictus, in the PROGRESS study. (18, 19)

WHAT WOULD BE THE REASONS FOR INCREASED USE OF HCTZ COMPARED WITH CT?

It seems that the reasons are unrelated to the pharmacological properties and the evidence in therapeutic trials. The final conclusions should be drawn from comparative and randomized trials, long enough to assess events, and including AMBP to determine the peak/valley relationship.

CONCLUSIONS

The prevalence of the use of HCTZ on CT has a mainly commercial origin, since HCTZ is more available either individually or in fixed combinations with beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. CT has been the most widely used diuretic in clinical trials that reported effective prevention of cardiovascular disease, with outstanding advantages in pharmacokinetics and blood pressure at equivalent doses. Even IP shows some comparative advantages. Some authors consider that CT should be preferred in future comparisons of antihypertensive drug combinations. (1) Prolonged half-life overlaps the effect of daily doses, and for that reason, lower doses of CT have similar antihypertensive and metabolic effects to those of higher doses of HCTZ. But the antihypertensive efficacy is greater with CT in daytime and nighttime response, and in long term treatment.

BIBLIOGRAPHY

1. Ernst ME, Moser M. Use of diuretics in patients with hypertension. N Engl J Med 2009; 361:2153-64.

2. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. Cardiol Rev 2010; 18:51-6.

3. Brunton LL, Lazo JS, Parker KL. Goodman & Gilman's. The pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006.

4. Ellison DH. Diuretic resistance: physiology and therapeutics. Semin Nephrol 1999; 19:581-97.

5. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 2004; 43:4-9.

6. Moser M, Sica D, Cushman W, Jamerson K. Diuretics as monotherapy or as part of combination therapy for hypertension: an update. J Clin Hypertens (Greenwich) 2008; 10:726-34.

7. Ceylan K, Topal C, Erkoc R, Sayarlioglu H, Can S, Yilmaz Y, et al. Effect of indapamide on urinary calcium excretion in patients with and without urinary stone disease. Ann Pharmacother 2005; 39:1034-8.

8. Mallion JM, Asmar R, Boutelant S, Guez D. Twenty-four hour antihypertensive efficacy of indapamide, 1.5-mg sustained release: results of two randomized double-blind controlled studies. J Cardiovasc Pharmacol 1998; 32:673-8.

9. Tweeddale MG, Ogilvie RL, Ruedy J. Antihypertensive and biochemical effects of chlorthalidone. Clin Pharmacol Ther 1977; 22:519-27.

10. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991; 265:3255-64.

11. Bowlus WE, Langford HG. A comparison of the antihypertensive effect of chlorthalidone and hydrochlorothiazide. Clin Pharmacol Ther 1964; 5:708-11.

12. Clark EC, Podolsky S, Thompson EJ. Double-blind comparison of hydrochlorothiazide plus triamterene therapy versus chlorthalidone therapy in hypertension. South Med J 1979; 72:798-802.

13. Khosla N, Elliott WJ, Bakris GL. Are chlorthalidone and hydrochlorothiazide equivalent blood pressure-lowering medications? J Clin Hypertens (Greenwich) 2005; 7:354-6.

14. Elliott WJ, Grimm RH Jr. Using diuretics in practice– one opinion. J Clin Hypertens (Greenwich) 2008; 10:856-62.

15. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006; 47:352-8.

16. Multiple Risk Factor Intervention Trial Research Group. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. Circulation 1990; 82:1616-28.

17. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 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.

18. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358:1887-98.

19. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, et al; Writing Committee for the PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke 2004; 35:116-21.