ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 6, 2015

ISSN - 0974-2441

Research Article

FIRST AMONG EQUALS: A COMPARATIVE STUDY OF THE EFFECT OF HYDROCHLOROTHIAZIDE AND CHLORTHALIDONE ON RECENTLY DIAGNOSED HYPERTENSIVES

BIJAY KUMAR, SHARANJIT KAUR*, SAMI MANZOOR, HARINDER JOT SINGH

Department of Pharmacology, Maharishi Markandeshwar Medical College and Hospital, Kumarhatti, Solan, Himachal Pradesh, India.

Email: drsharan25@gmail.com

Received: 28 July 2015, Revised and Accepted: 29 September 2015

ABSTRACT

Objective: Thiazide diuretics have been the first choice to treat stable, uncomplicated, essential hypertension; hydrochlorothiazide (HCTZ) being the most preferred. Another thiazide, chlorthalidone is available since long and is reported to be equally efficacious if not better in treating primary hypertension.

Aim: To compare the efficacy and safety of HCTZ and chlorthalidone in the management of primary essential hypertension.

Methods: We compared these two drugs in a randomized, single-blinded, intention to treat study. Participants with essential hypertension received either chlorthalidone 12.5 mg OD or HCTZ 25 mg OD for a period of 12-week. The results were compared on the basis of 12 hourly ambulatory blood pressure (BP) monitoring; fortnightly record of serum potassium, and failure of treatment (i.e., the need of additional antihypertensive drug or incrementation in the dose of thiazides).

Results: Out of 114,44 in chlorthalidone group and 39 in HCTZ group completed our study. There was a significant mean fall in BP by −11.89/−9.86 in the morning time and by −11.12/−7.56 in the evening time in group H receiving HCTZ 25 mg OD. In chlorthalidone group, this mean fall was by −16.45/−12.38 in the morning time and by −15.73/−10.86 in the evening time. After 12 weeks, night time BP control was better in chlorthalidone group (127.91±5.01) than HCTZ (132.67±5.19) (p=0.001). Both drugs decreased serum potassium levels, but this decrease was marginally more with HCTZ (3.777±0.601 vs. 3.891±0.534), statistically non-significant when compared to each other (p>0.05).

Conclusion: Chlorthalidone is better than HCTZ in controlling BP throughout the day without causing any significant complication.

Keywords: Diuretics, Antihypertensive effect, Hydrochlorothiazide, Chlorthalidone, Hypokalemia.

INTRODUCTION

Management of essential hypertension starts with advice regarding lifestyle changes and diet [1]. Pharmacotherapy is started when these measures fail or not heeded. If there is no contraindication, the first drug to be tried in these cases is a thiazide. Eighth Joint National Committee in 2014 recommends thiazides as the first choice even in diabetics [2]. ALLHAT trial suggests the same [3]. But, which thiazide? None is forthcoming.

Thiazide is diuretics; they prevent the reabsorption of sodium and chloride at distal convoluted tubules by interfering with sodium chloride transporter [4]. Their antihypertensive effect is due to: (a) Shrinkage of extracellular fluid and (b) their direct and indirect vasodilatory property. The latter effect is mainly responsible for its antihypertensive property [5].

Hydrochlorothiazide (HCTZ) and chlorthalidone share one another important property. Both have sulfonamide moiety in their structure which inhibits carbonic anhydrase enzyme enhancing to their diuretic effect [6]. Pharmacokinetically they differ. Chlorthalidone is more protein bound so longer acting (half-life - 40-60 hrs) and is twice as potent as HCTZ (half-life - 6-15 hrs) [7]. Inhibition of carbonic anhydrase is greater with chlorthalidone, and this inhibition has the additional beneficial effect on the cardiovascular system (CVS) and platelet function [8]. On chronic use, HCTZ is known to produce metabolic changes, i.e. dysglycemia and dyslipidemia. Chlorthalidone too produces these changes, but these are reported to be milder in comparison to HCTZ. Thiazides produce hypokalemia too, the intensity of which is reported to be less with chlorthalidone [9].

HCTZ and chlorthalidone are thiazides. This study was to find out which of the two is better suited to our population. This study was done to know the efficacy and safety of chlorthalidone in comparison to HCTZ.

METHODS

This study was conducted in Maharishi Markandeshwar Medical College and Hospital, Kumarhatti, Solan from 2013 to 2015. The protocol was approved by the Ethical Committee of the Hospital and was done according to the Good Clinical Practice guidelines and the Helsinki Declaration.

114 adult males requiring pharmacotherapy for hypertension for the first time were selected for the study. The participants for this study were screened from adults visiting various outpatient departments (OPD) of this hospital for minor ailments. We selected our participants who met eligibility criteria, i.e., (a) mild to moderate hypertensive with systolic blood pressure (SBP) >130 mm of Hg and diastolic BP (DBP) >90 mm of Hg, (b) requiring pharmacotherapy for hypertension for the first time, (c) age - 20-60 years, (d) body mass index: 20-29, (e) non-diabetic, (f) non-dyslipidemic and non-alcoholics, and (g) not suffering from any chronic disease. We ensured that participants were non-alcoholic and non-smokers.

A written consent was taken from all eligible interested participants. All selected participants were investigated for serum lipids, glucose, and potassium. The baseline findings were recorded. They were randomly assigned to take either HCTZ 25 mg OD (Group H) or chlorthalidone 12.5 mg OD (Group C) every morning 7.00 am.

Follow-up

The participants were taught to record their BP through a portable digital BP machine at 9 am and 9 pm every day and to maintain a record of it. They were asked to take these recordings in the supine position after 5 minutes of rest. They were encouraged to report fortnightly in the OPD for routine follow-up when their blood sample was taken for serum lipids, glucose, and potassium levels. Those who had needed intervention because of poor control of BP and those who developed adverse effect were dropped from the study (Table 1).

Statistics

The basic descriptive statistics were calculated and expressed as mean ± standard deviation. The data at baseline and at 12 weeks was compared by using *t* tests with a level of significance of 0.05. The statistical analysis was performed by using the software, SPSS 16.

RESULTS

114 participants consented and enrolled in this study, 57 each in HCTZ group (Group H) and chlorthalidone group (Group C). 83 participants completed this study. 10 participants (3 in chlorthalidone and 7 in HCTZ) were dropped from the study as their BP was poorly controlled, and clinicians felt the need of intervention in the form of either increasing the dose of respective thiazides or addition of another antihypertensive drug. One participant in HCTZ was dropped from the study as he had developed hypokalemia and hyperglycemia. Rest was not compliant.

Table 2 summarizes the baseline characteristics of all the individuals completing the study period.

During the study period (Table 2), total of 114 adult male patients were enrolled. Only 83 completed the study. The mean age in this study was 50.23±6.041 in Group H and 49.56±6.308 in Group C (p>0.05 NS). The SBP and the DBP were 144±6.601 mmHg and 94.923±5.464 mmHg at the baseline in Group H. In Group C, SBP was 145.681±6.583 and DBP 94.568±4.692 at the baseline (p>0.05). Two groups when compared for blood biochemistry in the form of serum glucose. Total cholesterol and potassium levels both were found to be comparable (p>0.05).

There was significant fall of both SBP and DBP in the morning and evening time in both the groups after 12 weeks of therapy as shown in Tables 3 and 4.

There was a mean fall in SBP by −11.898 and DBP by −9.869 in the morning time and by −11.127 and −7.564 in the evening time in Group H, whereas in Group C the mean fall was by −16.454 and −12.382 in the morning time and by −15.727 and −10.863 in the evening time.

After 12 weeks of therapy, morning BP control was better in Group C; SBP was 127.23±4.650 than in Group H where it was 130.10±4.610 (p<0.005). DBP came down too but was statistically not significant when compared with each other (Table 5).

The participants in Group C fared better than Group H in evening time BP control. After 12 weeks of treatment, mean BP in Group C was 127.91±5.011 while in Group H it was 132.67±5.198 (p=0.0001). DBP too was comparatively less in Group C than Group H (81.5±3.231 vs. 85.026±1.769) as shown in Graph 1.

Serum potassium levels were reduced in both groups after 12 weeks of therapy. In Group H, potassium levels came down from 4.210±0.473 to 3.777±0.601, while in Group C this fall was from 4.300±0.443 to 3.891±0.534 (p=0.001). However, this respective decrease in potassium levels was statistically not significant when results were compared to each other (p>0.05) (Table 6).

Serum potassium levels were reduced in both groups, but the mean fall was never below 3.5 mmol/L in both groups as shown in Graph 2.

Table 1: Selection of participants and interventions

Day 1
Eligible male patients 20-60 years of age group
SBP >130 mm of Hg and DBP >90 mm of Hg
No concomitant disease
Renal creatinine clearance <1.8 mg/dl
Months 1-2
Lifestyle modifications
Weight control
Low sodium intake
Physical activity and good sleep
Month 2
Randomization
Consent form
SBP >130 mm of Hg and DBP >90 mm of Hg
Blood test: Serum glucose, potassium, and lipids
Start with either HCTZ 25 mg OD or chlorthalidone 12.5 mg OD
Instructions for BP monitoring 12 hourly
Follow-up fortnightly (up to 12 weeks)

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HCTZ: Hydrochlorothiazide

Table 2: Baseline demographic characteristics of subjects completing the study period

Variable	Group H (n=39)	Group C (n=44)	p value
Age	50.23±6.041	49.56±6.308	>0.05*
BMI	25.58±50	26.58±24	>0.05*
Office SBP (mm of Hg)	144±6.601	145.681±6.583	>0.05*
Office DBP (mm of Hg)	94.923±5.464	94.568±4.692	>0.05*
Serum potassium levels	4.214±0.463	4.282±0.437	>0.05*
Fasting glucose, mg/dL	125.6±5.28	124.28±5.266	>0.05*
Cholesterol, mg/dL	216.23±4.34	215.8±4.28	>0.05*

*Non-significant. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3: BP reading in Group H (HCTZ 25 mg OD)

Group H	BP (mm of Hg)	At 2 weeks	At 12 weeks	p value
9 am	SBP	142±5.228	130.102±4.610	0.0001***
	DBP	91.920±5.464	82.051±3.568	0.0001***
9 pm	SBP	143.794±6.169	132.667±5.198	0.0001***
	DBP	92.589±4.678	85.025±1.769	0.0001***

***Extremely significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HCTZ: Hydrochlorothiazide

Table 4: BP reading in Group C (chlorthalidone 12.5 mg OD)

Group C	BP (mm of Hg)	At 2 weeks	At 12 weeks	p value
9 am	SBP	143.681±6.583	127.227±4.650	0.0001***
	DBP	90.568±4.692	80.590±2.975	0.0001***
9 pm	SBP	143.636±7.298	127.91±5.011	0.0001***
	DBP	92.363±4.861	81.5±3.231	0.0001***

***Extremely significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 5: 12 hourly BP control in both groups after 12 weeks of therapy

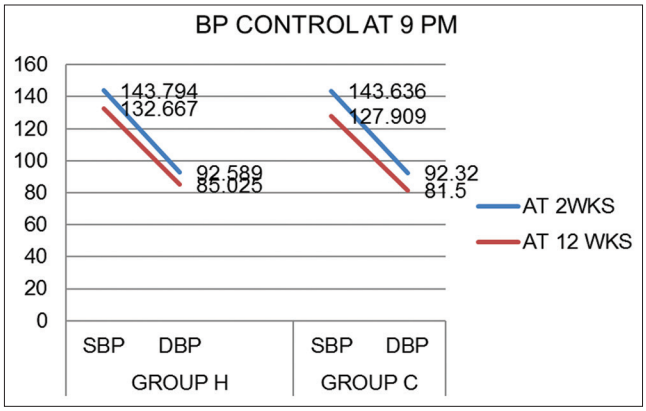
Time of recording BP	BP (mm of Hg)	Group H	Group C	p value
9 am	SBP	130.10±4.610	127.23±4.650	<0.005**
	DBP	82.051±3.568	80.590±2.975	>0.05NS
9 pm	SBP	132.67±5.198	127.91±5.011	<0.0001***
	DBP	85.026±1.769	81.5±3.231	<0.0001***

**Very significant, ***Extremely significant, NS: Non-significant, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

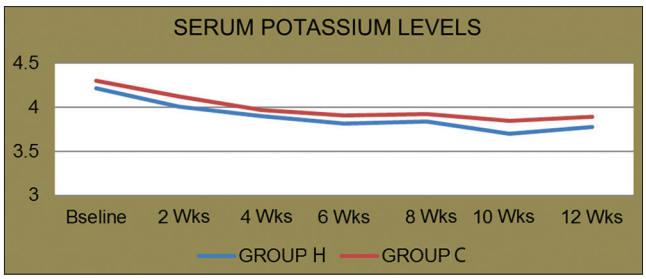
Table 6: Serum K+ levels at baseline and after 12 weeks

Serum K+ levels (mmol/L)	Baseline	At 12 weeks	p value
Group H	4.210±0.473	3.777±0.601	0.001***
Group C	4.300±0.443	3.891±0.534	0.001***

***Extremely significant



Graph 1: Blood pressure control at 9 pm in both groups



Graph 2: Serum potassium levels 2 weekly

DISCUSSION

Hypertension is an important primary intervention targeted to decrease the cardiovascular morbidity and mortality. Various studies are available with thiazides as antihypertensive drugs to confer the cardiovascular protection [10].

Most of the clinicians support the evidence that these two thiazides can be used interchangeably, but studies are available which shows that chlorthalidone is more potent than HCTZ due to differences in pharmacokinetic and pharmacodynamic features [6].

This more than 2 years study where participants with newly diagnosed hypertension were treated with either HCTZ or chlorthalidone and were closely followed for 12 weeks; we found that chlorthalidone treated patients fared much better in all parameters ascertained, i.e., diurnal BP control, incidence of hypokalemia, metabolic changes, and failure of therapy (need to increase the dose or need of additional anti-hypertensive drug).

Ernst *et al*. in 8 weeks study with same drugs found that there was a greater reduction from baseline SBP with chlorthalidone as compared with HCTZ (24 hrs ambulatory BP monitoring). 24-hrs mean SBP in chlorthalidone group was −12.4±1.8 mm Hg versus −7.4±1.7 mm Hg in HCTZ group (p=0.054) The reduction in SBP during nighttime hours was −13.5±1.9 mmHg for chlorthalidone versus −6.4±1.7 mmHg for HCTZ (p=0.009) [11].

Dorsch *et al*. comparing the patients treated with HCTZ or chlorthalidone in MRFIT trial found that mortality was higher in HCTZ group. MRFIT steering committee strongly recommended chlorthalidone than HCTZ in all interventions requiring antihypertensive treatment. In their secondary analysis of the same trial, they concluded chlorthalidone treated patients were less likely to have serious CVS events than HCTZ [12].

Roush *et al*. came to the same conclusion in their trial too, i.e. chlorthalidone is better than HCTZ in the treatment of hypertension. They concluded that chlorthalidone was superior to HCTZ in reducing congestive heart failure and in reducing all cardiovascular events (CVE). There was 21% less chance of CVE's with chlorthalidone than HCTZ [13].

Ernst *et al*. who has worked extensively on this very subject mentions that there is greater fluctuation in SBP in HCTZ treated patients, i.e., their nocturnal SBP tends to be higher in chlorthalidone treated patients [11]. Our study also shows this; chlorthalidone patients treated had lower nocturnal SBP.

Neff and Nawarskas pointed that there was less chance of hypokalemis with chlorthalidone than HCTZ. The results of their study were not significant statistically but considering the fact that potassium is chiefly an intracellular cation (150 mmol intracellular vs. 2.4 mmol extracellular), even this slight reduction in potassium levels becomes very important. Our contention is that this comparatively marginal less reduction of serum potassium is responsible for chlorthalidone producing less severe adverse effects. Metabolic changes that usually occurs during the course of a thiazide therapy is because of decreased serum potassium levels and since there is less reduction of serum potassium with chlorthalidone, theoretically less severe ADR should occur with this drug [14].

Dhalla *et al.* differs from our study regarding the decrease in serum potassium levels they concluded that chlorthalidone is responsible for more cases of hypokalemia than HCTZ. However, they agree to certain limitations in their study, i.e., the study was performed in older age group; participants were receiving additional anti-hypertensive drugs and were probably taking additional medication for various ailments from which geriatrics usually suffer. In all other studies, there was less reduction of potassium levels with chlorthalidone [15].

In our study, we found that chlorthalidone had a definitive edge over HCTZ and was better suited to control BP all day long. This is probably due to their longer half-life and their comparatively stronger ability to inhibit carbonic anhydrase enzyme. This greater inhibition of carbonic anhydrase gives chlorthalidone added advantage to decrease platelet aggregation and amplification of angiogenesis as demonstrated by the excellent work of Woodman *et al.* [8].

CONCLUSION

Chlorthalidone and not HCTZ should be the first choice to treat essential hypertension. Permit us to take a leaf out of George Orwell's famous book "Animal Farm" and confidently state: "Chlorthalidone is more equal than HCTZ for the primary pharmacotherapy in hypertension."

REFERENCES

1. Gupta R, Guptha S. Strategies for initial management of hypertension. Indian J Med Res 2010;132:531-42.
2. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al* 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-20.
3. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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):2981-97.
4. Ellison DH, Velázquez H, Wright FS. Thiazide-sensitive sodium chloride cotransport in early distal tubule. Am J Physiol 1987;253:F546-54.

5. Salvetti A, Ghiadoni L. Thiazide diuretics in the treatment of hypertension: An update. J Am Soc Nephrol 2006;17 4 Suppl 2:S25-9.
6. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: Evidence supporting their interchangeability. Hypertension 2004;43(1):4-9.
7. Sica DA. Chlorthalidone: Has it always been the best thiazide-type diuretic? Hypertension 2006;47(3):321-2.
8. Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. Hypertension 2010;56(3):463-70.
9. Ernst ME, Lund BC. Renewed interest in chlorthalidone: Evidence from the Veterans Health Administration. J Clin Hypertens (Greenwich) 2010;12(12):927-34.
10. Olde Engberink RH, Frenkel WJ, van den Bogaard B, Brewster LM, Vogt L, van den Born BJ. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: Systematic review and meta-analysis. Hypertension 2015;65(5):1033-40.
11. 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(3):352-8.
12. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: A retrospective cohort analysis. Hypertension 2011;57(4):689-94.
13. Roush GC, Buddharaju V, Ernst ME. Is chlorthalidone better than hydrochlorothiazide in reducing cardiovascular events in hypertensives? Curr Opin Cardiol 2013;28(4):426-32.
14. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. Cardiol Rev 2010;18(1):51-6.
15. Dhalla IA, Gomes T, Yao Z, Nagge J, Persaud N, Hellings C, *et al.* Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: A population-based cohort study. Ann Intern Med 2013;158(6):447-55.