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ORIGINAL ARTICLE

Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to candesartan in treatment-naïve patients of hypertension

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Thiazide-type diuretics are the most commonly used blood pressure (BP)-lowering drug for patients with uncomplicated hypertension. However, it has remained unclear whether hydrochlorothiazide (HCTZ) or chlorthalidone (CTD) shows better improvement in central aortic pressure. We conducted an open-label, randomized, prospective cross-over study with an 8-week active treatment (HCTZ of 25 mg with candesartan of 8 mg or CTD of 12.5 mg with candesartan of 8 mg) with a 4-week washout period (only candesartan during this period). Twenty-eight treatment-naïve patients of hypertension were enrolled (mean age: 50 ± 9 years, male: 44.4%). Central aortic pressure, pulse wave velocity (PWV), augmentation index (AIx) and other BP-derived parameters were measured. After 8 weeks of active treatment, there was no significant difference in changes of central aortic pressure between HCTZ and CTD treatments ($\Delta = -14 \pm 8$ vs. -16 ± 7 mm Hg, $P = 0.645$). However, CTD treatment showed a significant reduction in PWV compared with baseline (1321 ± 194 vs. 1439 ± 190 cm s^{-1}, $P = 0.007$) and HCTZ treatment ($\Delta = -118 \pm 82$ vs. $\Delta = 5 \pm 72$ cm s^{-1}, $P = 0.033$), whereas HCTZ treatment showed a marginal, but not a significant reduction in AIx compared with baseline. In conclusion, CTD of 12.5 mg is as potent as HCTZ of 25 mg, when combined with candesartan of 8 mg, in lowering central aortic pressure. In addition, CTD treatment resulted in a significant reduction of PWV.

INTRODUCTION

Although thiazide-type diuretics are a favored initial treatment option for patients with uncomplicated hypertension, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guideline does not specify which drug from this class is preferred.[1] Among thiazide-type diuretics, hydrochlorothiazide (HCTZ) in a daily dose of 12.5–25 mg has been widely employed as initial therapy for most patients with hypertension, but recently chlorthalidone (CTD) has regained clinical usage as a substitute for HCTZ because of better clinical outcomes and blood pressure (BP)-lowering effects.[2,3]

Although CTD and HCTZ are structurally similar compounds, they are quite dissimilar pharmacokinetically. CTD is distinguished from HCTZ in that the former has an extremely long half-life and a very large volume of distribution owing to its extensive partitioning into red blood cells.[4] CTD, at half the dose, is more effective in lowering systolic BP (SBP) than HCTZ, mainly because of its BP-lowering efficacy throughout the night time hours.[5] Therefore, it is

postulated that difference in persistence of BP-lowering efficacy would contribute to differences in central BP and arterial stiffness.

Whether these two drugs have different effects on clinical outcomes remains unclear, but evidence indicates that the benefit of low-dose thiazide-based regimens to reduce cardiovascular events is primarily derived from studies using CTD, whereas HCTZ is inferior to other classes of hypertensive drugs, including angiotensin-converting enzyme inhibitors[6] and calcium channel blockers.[7] Furthermore, a retrospective comparative analysis demonstrated that CTD reduces cardiovascular events more than HCTZ.[3] Therefore, a recent guideline recommended the use of CTD or indapamide in preference to HCTZ.[2]

The central arterial system serves as a conduit delivering blood to the organs and tissues, and acts as a 'buffer' by distending during cardiac ejection to provide an optimal and continuous peripheral blood flow.[8] The distending pressure in the large elastic arteries (aorta and carotid artery) is a key determinant of the degenerative changes that characterize accelerated aging and hypertension. In contrast,

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Of those, four were excluded because two suffered from dizziness and intolerance to the study drugs and the other two had withdrawn the consent form. Finally, of the 28 patients enrolled, 15 were initially allocated to the HCTZ/candesartan treatment and the remaining 13 were allocated to CTD/candesartan treatment. Of course, each group did cross-over to the other treatment combination.

Baseline characteristics of the patients are summarized in Table 1.

Changes of brachial BPs between the two antihypertensive treatment combinations

Patients were categorized into HCTZ/candesartan and CTD/candesartan assignments. After 8 weeks of the active treatment, both treatments achieved significant improvements in brachial SBP, DBP, PP, mean BP and rate-pressure product compared with baseline (Table 2). Only the HCTZ/candesartan treatment showed a significant increase in HR. However, there was no significant difference in changes of brachial BP and BP-derived parameters between the two therapies.

Changes of central BPs between the two antihypertensive treatment combinations

A significant order-drug-time interaction implied the order in which the two drugs were given had a significant effect on differences of the magnitude of change in central SBP between the two drugs. After the planned patients completed both active treatments, an order-drug-time interaction was found not to be significant ($P = 0.170$, data not shown). Moreover, a carryover effect was found not to be significant ($P = 0.395$, data not shown). This ensured that there was an adequate washout period.

After 8 weeks of active treatment, both drug combinations showed significant improvements in central SBP, DBP, PP and mean BP (Table 3). Fractional PP and pulsatility index were marginally reduced

with HCTZ/candesartan, but this was not significant. Rate-pressure product was significantly improved with CTD/candesartan treatment compared with baseline. However, there was no significant difference between the two treatment regarding changes in central BP or changes in BP-derived parameters.

Changes in aortic stiffness between the two antihypertensive treatment combinations

After 8 weeks of active treatment, the CTD/candesartan treatment showed a significant reduction in PWV compared with baseline and the HCTZ/candesartan treatment, whereas the HCTZ/candesartan treatment showed a marginal, but nonsignificant, reduction in AIx and AIx@75 compared with baseline (Table 4).

Table 1 Baseline characteristics of study patients

Variable	All subjects (n = 28)
Age (year)	50 ± 9
Male, *n* (%)	13 (46.4)
Office SBP (mm Hg)	152 ± 13
Office DBP (mm Hg)	94 ± 8
Height (m)	1.60 ± 0.08
Body mass index, kg m^{-2}	25.7 ± 2.2
Current smoker, *n* (%)	8 (28.6)
Hyperlipidemia, *n* (%)	13 (46.4)
Hemoglobin (mg dl^{-1})	14.0 ± 1.0
Fasting glucose (mg dl^{-1})	101.5 ± 12.8
Serum creatinine (mg dl^{-1})	0.87 ± 0.20
Glomerular filtration rate (ml min^{-1} 1.73 m^{-2}, by MDRD formula)	86.8 ± 12.6
Serum sodium (mEq l^{-1})	143 ± 2
Serum potassium (mEq l^{-1})	4.1 ± 0.3
Hs-CRP (mg dl^{-1})	0.22 ± 0.26
Cholesterol (mg dl^{-1})	
Total	215 ± 49
Low-density lipoprotein	134 ± 37
High-density lipoprotein	53 ± 12
Triglyceride	136 ± 73

Abbreviations: DBP, diastolic blood pressure; Hs-CRP, high-sensitivity C-reactive protein; MDRD, Modification of Diet in Renal Disease Study Group; SBP, systolic blood pressure. Values are the mean ± s.d. or a number (percentage).

Table 2 Changes in brachial BPs in the HCTZ/candesartan and CTD/candesartan groups

Variables (Brachia BPs)	HCTZ/candesartan	CTD/candesartan	P
SBP (mm Hg)			
Baseline (0 week)	128 ± 14	131 ± 12	0.831
End of study (8 week)	119 ± 11	116 ± 11	0.350
Change (95% CI)	−9 (−16 to −2)*	−15 (−22 to −9)*	0.194
DBP (mm Hg)			
Baseline (0 week)	81 ± 11	84 ± 9	0.688
End of study (8 weeks)	76 ± 10	74 ± 8	0.270
Change (95% CI)	−6 (−10 to −1)*	−10 (−14 to −6)*	0.148
PP (mm Hg)			
Baseline (0 week)	48 ± 10	48 ± 7	0.472
End of study (8 weeks)	43 ± 6	43 ± 7	0.923
Change (95% CI)	−5 (−10 to −1)*	−5 (−8 to −2)*	0.985
MBP (mm Hg)			
Baseline (0 week)	99 ± 12	100 ± 10	0.962
End of study (8 weeks)	90 ± 9	89 ± 10	0.669
Change (95% CI)	−8 (−14 to −3)*	−11 (−17 to −5)*	0.487
FPP			
Baseline (0 week)	0.49 ± 0.10	0.48 ± 0.06	0.417
End of study (8 weeks)	0.48 ± 0.08	0.48 ± 0.07	0.803
Change (95% CI)	−0.01 (−0.06 to 0.03)	0.00 (−0.02 to 0.03)	0.555
PI			
Baseline (0 week)	0.60 ± 0.15	0.58 ± 0.09	0.360
End of study (8 weeks)	0.57 ± 0.11	0.58 ± 0.11	0.643
Change (95% CI)	−0.03 (−0.09 to 0.03)	0.00 (−0.03 to 0.04)	0.305
Heart rate (b.p.m.)			
Baseline (0 week)	71 ± 10	73 ± 10	0.333
End of study (8 weeks)	75 ± 13	73 ± 12	0.456
Change (95% CI)	5 (0 to 9)*	0.0 (−5 to 4)	0.092
RPP (mm Hg· b.p.m.)			
Baseline (0 week)	91 ± 18	96 ± 16	0.445
End of study (8 weeks)	82 ± 13	80 ± 15	0.500
Change (95% CI)	−9 (−15 to −2)*	−17 (−25 to −8)*	0.140

Abbreviations: BP, blood pressure; CI, confidence interval; CTD, chlorthalidone; DBP, diastolic blood pressure; FPP, fractional pulse pressure defined as the ratio of PP of MBP; HCTZ, hydrochlorothiazide; MBP, mean blood pressure; PI, pulsatility index defined as the ratio of PP to DBP; PP, pulse pressure; RPP, rate-pressure product (heart rate × SBP/10^2); SBP, systolic blood pressure.
*$P < 0.05$ *vs.* baseline.
Values are the mean ± s.d. or mean (95% CI).

Table 3 Changes in central BPs in the HCTZ/candesartan and CTD/candesartan groups

Variables (central BPs)	HCTZ/candesartan	CTD/candesartan	P
Central SBP (mm Hg)			
Baseline (0 week)	137 ± 16	138 ± 14	0.702
End of study (8 weeks)	123 ± 12	122 ± 13	0.687
Change (95% CI)	−14 (−22 to −6)*	−16 (−23 to −9)*	0.645
Central DBP (mm Hg)			
Baseline (0 week)	82 ± 11	85 ± 9	0.688
End of study (8 weeks)	77 ± 10	75 ± 8	0.270
Change	−6 (−10 to −1)*	−10 (−14 to −6)*	0.148
Central PP (mm Hg)			
Baseline (0 week)	54 ± 11	53 ± 10	0.347
End of study (8 weeks)	46 ± 9	47 ± 9	0.595
Change (95% CI)	−8 (−13 to −3)*	−6 (−10 to −2)*	0.501
Central MBP (mm Hg)			
Baseline (0 week)	100 ± 12	103 ± 10	0.942
End of study (8 weeks)	92 ± 9	90 ± 9	0.380
Change (95% CI)	−8 (−14 to −3)*	−12 (−17 to −7)*	0.290
FPP			
Baseline (0 week)	0.54 ± 0.10	0.52 ± 0.08	0.265
End of study (8 weeks)	0.50 ± 0.10	0.52 ± 0.08	0.395
Change	−0.04 (−0.08 to 0.00)	0.00 (−0.03 to 0.03)	0.122
PI			
Baseline (0 week)	0.67 ± 0.15	0.64 ± 0.12	0.240
End of study (8 weeks)	0.61 ± 0.15	0.64 ± 0.12	0.394
Change (95% CI)	−0.06 (−0.11 to 0.00)	0.00 (−0.04 to 0.05)	0.102
PP amplification			
Baseline (0 week)	0.90 ± 0.18	0.91 ± 0.12	0.762
End of study (8 weeks)	0.95 ± 0.21	0.91 ± 0.15	0.457
Change (95% CI)	0.05 (−0.07 to 0.19)	0.00 (−0.05 to 0.07)	0.480
RPP (mm Hg·b.p.m.)			
Baseline (0 week)	97 ± 20	101 ± 16	0.705
End of study (8 weeks)	92 ± 15	89 ± 17	0.404
Change (95% CI)	−5 (−12 to 2)	−12 (−20 to −4)*	0.152

Abbreviations: BP, blood pressure; CI, confidence interval; CTD, chlorthalidone; DBP, diastolic blood pressure; FPP, fractional pulse pressure defined as the ratio of PP of MBP; HCTZ, hydrochlorothiazide; MBP, mean blood pressure; PI, pulsatility index defined as the ratio of PP to DBP; PP, pulse pressure defined as the ratio of brachial PP to central PP; RPP, rate-pressure product (heart rate × SBP/10^2); SBP, systolic blood pressure.
*$P < 0.05$ vs. baseline.
Values are the mean ± s.d. or mean (95% CI).

Table 4 Changes in aortic stiffness in the HCTZ/candesartan and CTD/candesartan groups

Variables (Central BPs)	HCTZ/candesartan	CTD/candesartan	P
baPWV (m s^{-1})			
Baseline (0 week)	1377 ± 192	1439 ± 190	0.605
End of study (8 weeks)	1382 ± 220	1321 ± 194	0.173
Change (95% CI)	5 (−77 to 87)	−118 (−200 to −36)*,†	0.033
AIx (%)			
Baseline (0 week)	83 ± 11	79 ± 11	0.143
End of study (8 weeks)	78 ± 15	79 ± 13	0.849
Change (95% CI)	−5 (−11 to 0)	0 (−5 to 4)	0.150
AIx@75 (%)			
Baseline (0 week)	81 ± 11	78 ± 10	0.190
End of study (8 weeks)	77 ± 12	78 ± 13	0.321
Change (95% CI)	−5 (−10 to 0)	0 (−4 to 4)	0.131

Abbreviations: AIx, augmentation index; AIx@75, AIx adjusted for an heart rate of 75 b.p.m.; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; CTD, chlorthalidone; HCTZ, hydrochlorothiazide.
*$P < 0.05$ vs. baseline and †$P < 0.05$ vs. HCTZ/candesartan.
Values are the mean ± s.d. or mean (95% CI).

of aortic pressure waveforms based on pressure recordings at the radial artery.[24] The correspondence between calculated and directly recorded central BP has been found to be within 1 mm Hg.[25–27]

Several potential mechanisms could explain the reason why there were no differences in central BPs between HCTZ and CTD treatment in our study. First, it is possible that candesartan might lessen the effect of thiazide-type diuretics. It is known that various anti-hypertensive drugs have differential effects on central SBP, despite their similar effects on brachial SBP.[12,28–32] Indeed, inhibitors of the renin-angiotensin system cause a greater fall in central BP.[31,33] However, diuretics are not as effective as vasodilating drugs in reducing central SBP,[29,34] because they poorly modify the micro-vascular structure.[35] Angiotensin receptor blockers are one of the first-line antihypertensive drugs for most patients, but mono-therapy achieves the target BP that is recommended by the treatment guidelines[36,37] in only a limited number of patients. Thus, combination therapy is required in a majority of patients.[36] A thiazide-type diuretic is commonly used in combination with angiotensin receptor blocker because it has an additive effect on BP reduction due to the complementary mechanisms of action of the components,[36] and the efficacy of this combination has been demonstrated in many clinical trials.[32,38,39] Although we designed a comparison adopting combination drugs rather than diuretics alone to reflect real-world antihypertensive therapy, angiotensin receptor blockers might have attenuated the effect of diuretics on central BP. Second, central aortic pressure is dependent not only on PWV but also on AIx.[40] The reduction in PWV and AIx has a significant role in central SBP reduction. Therefore, the different responses of two hemodynamic measurements in our study may explain why the central BPs were not different between HCTZ and CTD treatment. Third, an increase in HR is associated with lower central aortic pressure.[12,28,31,34] Our study displayed HR increases in HCTZ treatment, which may cause a potential bias and contribute to an unexpected result. Fourth, a previous study demonstrated that the CTD was more effective in lowering BP during night time hours than HCTZ, but failed to show any difference in office BP and BP during the day time hours.[5] Therefore, the measurement of central aortic pressure in day time

DISCUSSION

The main finding of this study was that changes in central BPs were not significantly different between the HCTZ (25 mg per day) and CTD (12.5 mg per day) treatment combined with candesartan after an 8-week active treatment.

Central BP can be measured invasively by the use of a catheter (fluid-filled or high-fidelity micro-tip pressure transducers), but it has not got widespread use in large epidemiological studies and in daily clinical practice because of technical limitations and high costs. In contrast, noninvasive techniques have provided a great impetus for the spread of central pressure estimation in clinical practice. The application of generalized transfer functions for the indirect estimation

had an inherent limitation, but measuring central BP during the night time has been unavailable.

Our study has several strengths and implications. First, to our knowledge, our trial is the first study to compare the effect on central BPs between HCTZ and CTD. Our results lend further support to the notion that HCTZ and CTD, using half the dose of HCTZ, present similar BP-lowering efficacy even in central BP.

Second, interestingly, the impact on arterial stiffness between the two treatments displayed different results depending on the evaluation methods. The PWV is likely to be a better measure in older individuals (>50 years) but AIx might be a more sensitive marker in younger individuals (<50 years).[41] Taken together, we assume that there is a different response between the HCTZ and CTD according to age in terms of arterial stiffness. Anyway, CTD treatment significantly reduced PWV compared with baseline and HCTZ, whereas HCTZ shows a trend toward reduction of AIx.

The increased arterial stiffness is believed to originate from a medial calcification,[42] and a correlation between PWV and large artery calcification has been shown.[43] Thiazide-like diuretic is known to inhibit carbonic anhydrase, the major source of protons used by osteoclasts, resulting in inhibition of medial calcification,[44] and CTD more potently inhibits carbonic anhydrase than HCTZ.[45] Therefore, this may explain a greater decline in PWV during CTD treatment. Vascular stiffness may better summate chronic damage to blood vessels from aging, hypertension and diabetes than brachial or even central BP.[11] PWV has been related to cardiovascular risk in hypertensive patients,[46] the elderly,[47] patients with end-stage renal disease[48] and population-based samples.[49] Therefore, better reduction in PWV than HCTZ may contribute to decrease in cardiovascular events.

The beneficial effect on AIx in the HCTZ treatment can be explained, at least in part, by a substantial increase in HR. HR is an independent determinant of AIx and an increase in HR can result in a decrease in AIx.[18] However, AIx@75 that is independent of the HR influence also showed a marginal decrease in our study.

Third, there are only a few fixed-dose antihypertensive combinations that contain CTD, whereas HCTZ combo drugs are abundant.[4] Because CTD treatment causes similar reductions in central aortic pressure and peripheral BP with half the dose of HCTZ, manufacturing fixed-dose combinations containing CTD should be more prevalent.

There are limitations to our study. First, although the power calculation was based on anticipated central pressure difference, the study population was too small to detect significant difference in central BP, given the large s.d. Based on our results, over 500 subjects would be needed to show a superiority of CTD in reduction in central BP. Second, the study period was relatively short. It is important to evaluate longer-term treatment to clarify the effect of these combination therapies on central aortic pressure. Third, a potential weakness is that the calibration of central aortic pressures depends on the accuracy of the brachial pressure measurement.[50,51] Forth, we compared only two commonly used doses of each drug, and it is unclear whether no difference in central BPs would persist in other doses. Fifth, this was not a double-blind study. However, the open-label, randomized, prospective cross-over, blinded end-point design is often used, and if it is designed and conducted properly, the results are not thought to be biased.[52] Moreover, all of the critical measurements were performed by an investigator who was blinded to treatment allocations. Sixth, pretreatment with angiotensin receptor blocker might create a bias in patient selection. Seventh, the development of hypokalemia, major side effect, was not compared. Eighth, our study population was limited to Asians and results may not be applicable to other populations.

CONCLUSION

Our study compared the antihypertensive efficacy of usual recommended doses of HCTZ (25 mg per day) and CTD (12.5 mg per day) on central aortic pressure. We found that CTD, at half the dose, is as potent as HCTZ (both combined with candesartan) in lowering central aortic pressure. In addition, CTD resulted in a significant reduction in PWV, whereas HCTZ showed a trend toward reduction of AIx.

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