Original Article

Comparative Efficacy of Hydrochlorthiazide and Chlorthalidone, used either alone or in Combination Therapy in Patients with Essential Hypertension in Tertiary Care Hospital of Uttrakhand

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Aims : To study the comparative efficacy of Hydrochlorothiazide and Chlorthalidone, either used alone or in combination on Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Lipid Profile and Anthropometry.

Methods : It was a Prospective, Randomised, Longitudinal study, where consecutive patients presenting to medicine Out Patient Department (OPD) and In Patient Department (IPD) were screened for essential hypertension based upon the JNC VII Guidelines. Those subjects who satisfy the inclusion and exclusion criterias were included in the study. These subjects were divided into four subgroups. Each patient was assessed for Blood Pressure (BP), Lipid profile, Anthropometry for a period of 180 days.

Results : There was statistically significant reduction in both systolic blood pressure and DBP in both the groups over a period of 180 days. This trend was progressive during the observed period in both the groups till a stable state was reached. There was a greater reduction in the SBP in the chlorthalidone group as compared to the Hydrochlorothiazide group (P value 0.05). However, such trend was not observed on the DBP on the two groups. Over a six months follow up there was no change in the Lipid parameters either on the same group or while comparing the two groups. The body Anthropometry , especially waist Hip ratio and Body Mass Index also did not show any significant difference in the two groups(either used alone or in combination).

Conclusion : Chlorthalidone was found to be a relatively more potent Anti-hypertensive on SBP when compared with Hydrochlorothiazide .Both these drugs failed to show any significant difference in the Lipid Profile and Anthropometry in a period of six months.

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Key words **: Systolic Blood Pressure, Diastolic Blood Pressure, Hydrochlorithiazide, Chlorthalidone, Joint National Commitee.**

Hypertension is a Global Pandemic which has not respected the boundaries .Prevalence varying from 3.80-32.8% in men and 1.45-39.4% in women in the Urban areas and 1.57 to 36% in men and 2.38-37.21% in women in the Rural areas of India have been reported.

Recently an interest has been generated in the use of Chlorthalidone and Hydrochlorothiazide as an anti-hypertensive used alone or in combination with other anti-hypertensive agents. These two drugs came into existence almost simultaneously (Hydrochlorothiazide established in 1959 and Chlorthalidone in 1960) and had similar efficacy in terms of anti-hypertensive effect.

Hydrochlorothiazide and Chlorthalidone differ significantly in chemical structure but both contain a sulfonamide group that inhibits carbonic anhydrase activity, which may be associated with lower vascular contractility. Both drugs are concentrated in the Kidney and secreted into the Tubular Lumen[1]; therefore, their Therapeutic Diuretic Effects are often achieved with relatively Low Plasma Concentrations.

Low-dose Thiazide-type diuretics are recommended as initial therapy for most hypertensive patients. Chlorthalidone has significantly reduced Stroke and Cardiovascular End Points in several landmark trials; however, Hydrochlorothiazide remains favored in practice. Most clinicians assume that the drugs are interchangeable but their anti-hypertensive effects at lower doses have not been directly compared.The

Editor's Comment :

- Both these compounds were discovered at almost the same time with almost similar pharmacological profile.
- Both showed significant reduction of systolic and diastolic blood pressure. The reduction of systolic blood pressure was more statistically with chlorthalidone as compared to hydrochlorthiazide. The reduction in diastolic blood pressure was similar with the two drugs.
- There was no significant difference with these two drugs with respect to lipid profile and anthropometry.

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perspective of the study was to explore the strength and weakness of the two groups including their effects on various parameters effecting themorbidity and mortality.

Aims and Objectives

(1) To study the comparative efficacy of Hydrochlorothiazide and Chlorthalidone, either used alone or in combination on Systolic and DBP.

(2) To study the comparative efficacy of Hydrochlorothiazide and Chlorthalidone, either used alone or in combination on Lipid profile.

(3) To study the comparative efficacy of Hydrochlorothiazide and Chlorthalidone, either used alone or in combination and their effect on anthropometry

Material and Methods

The study was a Prospective, Randomised, Longitudinal study in the Department of internal medicine in Sri Guru Ram Rai Institute of Medical and Health Sciences and Sri Mahant and Indresh Hospital (SMIH), Dehradun where consecutive patients presenting to Medicine OPD and IPD were screened for essential Hypertension based upon the JNC VII Guidelines. Those subjects who satisfy the inclusion and exclusion criterias were included in the study. These subjects were divided into four subgroups

GROUP 1 : would include patients on Hydrochlorothiazidealone. GROUP 2: would include patients on Chlorthalidone alone.

GROUP 3 : would includepatients on Hydrochlorothiazide in Combination Therapy with other Anti-hypertensive .

GROUP 4 : would include patients on chlorthalidone in combination therapy with another anti-hypertensive.

Each patient was assessed for Blood Pressure, Lipid Profile, Anthropometry for a period of 180 days.

Results

There was statistically significant reduction in both Systolic Blood Pressure and Diastolic Blood Pressure in both the groups over a period of 180 days . This trend was progressive during the observed period in both the groups till a stable state was reached. It was interesting to observe that the reduction in the Systolic Blood Pressure was insignificant in the Hydrochlorothiazide and Chlorthalidone group until day 15 and the difference became significant beyond 30 days (Table 1). This clearly implies a greater reduction in the Systolic Blood Pressure in the Chlorthalidone group as compared to the Hydrochlorothiazide group. However, such trend was not observed on the Diastolic Blood Pressure on the two groups (Table 2). Also the serial reduction in Blood Pressure in the Hydrochlorothiazide and Chlorthalidone group was not as gradual and significant as was observed with the Systolic Blood Pressure. Over a six months follow up there was no change in the Lipid Parameters either on the same group or while comparing the two groups.

Table 1 — *Comparative Evaluation of Systolic Blood Pressure in Patients on HCTZ and CTD Used Alone (Group 1 and 2) and in Combination (Group 3 And 4)*

	Day 0 (a)	Day 15 (b)	Day 30 (c)	Day 60 (d)	Day 120 (e)	Day 180 (f)	P Value
GP 1	152.4 ± 5.42	148.65 ± 6.57	147.59 ± 5.07	144.78 ± 4.64	141.48 ± 5.15	138.41 ± 4.73	a-b<0.05 b-c>0.05 c-d<0.05 d-e<0.05 e-f<0.05
GP2	150.99 ± 6.49	145.68 ± 5.28	144.07 ± 5.76	140.56 ± 5.28	138.48 ± 5.21	133.96 ± 5.17	a-b<0.05 b-c<0.05 c-d<0.05 d-e<0.05 e-f<0.05
P Value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
GP 3	153.73 ± 6.07	149.09 ± 5.59	148.53 ± 5.68	144.30 ± 4.44	138.53 ± 4.39	132.24 ± 4.14	a-b<0.05 b-c>0.05 c-d<0.05 d-e<0.05 e-f<0.05
GP 4	152.44 ± 5.49	147.16 ± 5.21	144.75 ± 4.52	140.81 ± 3.44	135.98 ± 4.36	132.35 ± 4.13	a-b<0.05 b-c<0.05 c-d<0.05 d-e<0.05 e-f<0.05
P Value	>0.05	>0.05	<0.05	<0.05	>0.05	<0.05	

Table 2 — *Comparative Evaluation of Diastolic Blood Pressure in Patients on HCTZ and CTD Used Alone (Group 1 and 2)*

	Day 0 (a)	Day 15 (b)	Day 30 (c)	Day 60 (d)	Day 120 (e)	Day 180 (f)	P Value
GP 1	92.59 ± 4.47	91.15 ± 4.32	91.15 ± 3.26	90.42 ± 3.27	89.63 ± 1.93	85.42 ± 5.09	a-b<0.05 b-c>0.05 c-d>0.05 d-e>0.05 e-f<0.05
GP2	93.52 ± 4.43	90.00 ± 3.65	90.50 ± 3.04	89.59 ± 3.51	87.97 ± 4.35	84.23 ± 4.98	a-b<0.05 b-c>0.05 c-d<0.05 d-e<0.01 e-f <0.05
P Value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	
GP 3	92.55 ± 3.66	89.69± 4.54	88.82 ± 3.25	90.00 ± 00	88.24 ± 3.85	81.90 ± 3.97	a-b<0.05 b-c>0.05 c-d<0.05 d-e<0.05 e-f<0.05
GP 4	92.44 ± 4.35	90.27± 1.64	89.50 ± 1.52	90.00 ± 00	86.59 ± 4.80	81.39 ± 3.51	a-b<0.05 b-c<0.05 c-d<0.05 d-e<0.05 e-f<0.05
P Value	>0.05	>0.05	<0.05	>0.05	>0.05	>0.05	

The body Anthropometry, especially waist Hip Ratio and Body Mass Index (BMI) also did not show any significant difference in the two groups (either used alone or in combination) (Figs 1 & 2).

Discussion

The study was planned with the background that the Thiazide Group of diuretics are often considered a homogenous therapeutic class, where all Agents reduce Blood Pressure consistently and also reduce life threatening events including Cardiovascular Risks. While Hydrochlorothiazide is a prototype Thiazide, Chlorthalidone is a thalimide persisting Distinct Pharmacokinetics. Whether this unique effect results in Meaningful Pharmacodynamic Differences in hypertensive patients needed active evaluation.

The two drugs in the same class where developed around 1957 (Hydrochorthiazide in 1957 and Chlorthalidone two years later) although they were developed at almost the same time but probably due to different marketing strategies, Hydrochlorothiazide became more popular in united states and Chlorthalidone in United Kingdom. India has followed the American Trend. The idea of this study was to further evaluate whether the Thiazide group is truly a homogenous group as recommended by the Joint National Committee or are there Intergroup Differences both in relation to the Systolic and Diastolic Blood pressure and also the effect on the Lipid Profile.

On comparing group 1 and group 2 it can be seen that at the beginning of the study they were matched for age, sex, mean duration of illness, Systolic Blood Pressure, Diastolic Blood Pressure, Lipid Profile and Anthropometry. In group 1 females outnumbered males (15:12) with a mean duration of illness of 4.2 ±2.1

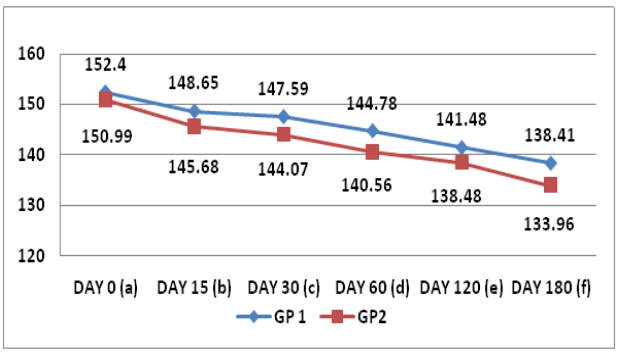

Fig 1 — SBP Changes (Group 1 *versus* 2)

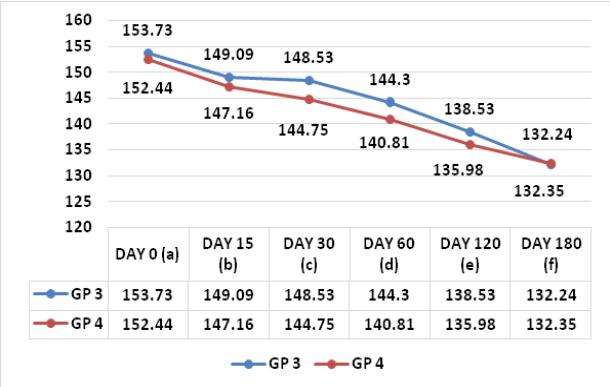

Fig 2 — SBP Changes (Group 3 *versus* 4)

years. Similarly , in subjects on Chlorthalidone (Group 2), females outnumbered males (50:31) with the mean duration of illness 4.8±1.8 years and hence the groups were comparable.

There was statistically significant reduction in both Systolic Blood Pressure and Diastolic Blood Pressure in both the groups over a period of 180 days (Tables 1 & 2). This trend was progressive during the observed period in both the groups till a stable state was reached. The serial reduction in Diastolic Blood Pressure in the Hydrochlorothiazide and Chlorthalidone group was not as gradual and significant as was observed with the Systolic Blood Pressure. The similar results were observed by Michael E Ernst *et al* where the reduction was more in the Systolic Blood Pressure in the Chlorthalidone Group[2].

It is known, that in the long term, Thiazide diuretics appear to reduce Blood Pressure by reducing peripheral resistance rather than by their diuretic effects[3], suggesting a Direct Vascular Dilating Action. Concentration-dependent relaxant effects of HCTZ have been demonstrated in animal and humanvascular smooth muscles. Mironneau et al. reported that HCTZ and Chlorthalidone, depressed isometric contractions, calcium contractures and membrane potentials in isolated longitudinal strips from Rat Portal Veins and suggested that this action was related to a decrease in the transmembrane Ca2+ influx. It has also been shown that HCTZ and CTD had direct relaxing actions in human subcutaneous resistance Arteries and that this action could be mediated by the Ca2+-activated K+ channel K(Ca2+)[4,5]. This vasodilator activity was also related to a decrease in intracellular Ca2+. In vivo, HCTZ at supra-therapeutic doses (3.5 0.3 lg/mL) exerted no vasodilator action in the human forearm[6]. However, at higher doses (11.0 1.6 lg/mL) HCTZ Demonstrated a Small Vasodilator Effect in the human forearm that was inhibited by tetraethylammonium, suggesting the involvement of vascular K(Ca2+) channels in these effects . At present, however, there is no concluding evidence to explain the decrease in Blood Pressure during the long-term treatment with HCTZ and CTD. On the other hand, it is known that Chlorothiazide causes a sustained raise in intracellular Ca2+ in distal convoluted and connecting tubules that is due to a Dihydropiridine-sensitive Calcium Influx through a Ca2+ channel composed of a1C and b3 subunits[7]. Also, little is known about the Cardiac cellular actions of Thiazide diuretics.

Also, those who were within 10 mm Hg goals Systolic Blood Pressure, had a higher likelihood of achieving goal Blood Pressure after they changed to Chlorthalidone. This difference may be attributed to a longer half-life of Chlorthalidone (45-60hours) in comparison to shorter acting Hydrochlorothiazide (half-life : 8 - 15) hours. In Hypertension detection and follow up programme Norman M Kaplan observed that in addition to the Blood Pressure control the mortality and morbidity was higher in hydrochlorothiazide group as with equivalent doses of Chlorthalidone Further the reduction in Diastolic Blood Pressure was not as satisfactory as the reduction in Systolic Blood Pressure[8].

Both these diuretics are commonly used in low doses in combination with other drugs. Most of the trails compared the mortality outcomes, only a few of them had head on compared the anti-hypertensive efficacy of this class. In combination as well, the reduction in the Systolic Blood Pressure was not as robust as when they were used alone. They showed a trend towards more reduction in Chlorthalidone group and this was observed maximum till 60 days. This is attributed to the fact that Chlorthalidone is 1.5 to 2 times more potent than Hydrochlorothiazide, although the observation by Norman N Kaplan was seen during the Ambulatory Blood Pressure Monitoring, In-clinic Monitoring showed a trend in favour of chlorthalidone (Table 1). As with the drugs when used alone the combination did show a consistent difference in Diastolic Blood Pressure Reduction. Possible mechanism of action include direct endothelial and vascular smooth muscle mediated vasodilatation and indirect compensation to acute decrease in the Cardiac output.

In our study an attempt was made to compare the effect of the two groups on Lipid Parameters. Over a six months follow up there was no change in the Lipid Parameters either on the same group or while comparing the two groups. Most of the studies like P. Weidmann et al. (1992), Richard P Ames *et al*, Thomas Pollare *et al*(1989), P Leren *et al*, showed an alteration in the Lipid Profile both in long term and short term[9]. The subjects in the either groups did not depict any significant difference in the Lipid Parmeters. This might be due to the fact that both the arms of the study were on the Lipid lowering medications in the form of statins. However, it has been observed that both Thiazide and Chlorthalidone alter Lipid parameters by increasing Plasma Triglycerides, Total Cholesterol and Low Density Lipoprotein on Hypertensive Subjects.

The diabetogenic potential of Thiazides has been implicated for single, as well as Combination Therapy. It has been attributed to increase hepatic glucose production, impaired peripheral glucose uptake, and

Hypokalaemia Mediated Beta Cell Dysfunction. Thiazides are effective in inhibiting sodium transport at the tubule in the Mammalian Nephron and hence decrease water retention[10].

Krum *et al* (2003) also did not observe any alteration in the Lipid Profile. The main findings of his study related to the impact of differing diuretic regimes melabolic parameters, and his findings did not support the suggestion that Thiazide diuretics when used in treatment of Hypertension may adversely effect the profile[10]. Hydrochlorothiazide was not associated with significant changes total Cholesterol, HDL Cholesterol and Apolipoprotiens. Indeed he observed Triglycerides levels increased significantly more with Hydrochlorthiazide Thiazides in high dosage and loop-diuretics can increase serum Low-Density-Lipoprotein cholesterol (LDL-C) and/or very-LDL-C and the total C/high-density Lipoprotein Cholesterol (HDL-C) ratio, while HDL-C is largely unchanged; triglycerides (TG) are also often elevated. Theories to explain these metabolic disturbances including increased Visceral Adiposity, Hyperurecemia, Decreased glucose Metabolism and Pancreatic Beta Cell Hyperpolarisation, may play a role.

The body Anthropometry, especially Waist Hip Ratio and Body Mass Index also did not show any significant difference in the two groups (either used alone or in combination). Although both these classes of drugs increase the basal insulin concentration and delay the insulin sensitivity response to glucose.

There are no head on trials found in literature which compared the Anthropometryin the two groups, however in this study the subjects in both the groups where on Lipid Modifying Drugs, especially statins It may be observed that anti-hypertensives do also have Lipid Modifying properties .But it can certainly inferred that despite being the modifier in both the arms, there was no significant difference on the Anthropometry and the lipid profile on subjects Hydrochlorothiazide and Chlorthalidone. Secondly it may be considered that the alteration in the Lipid Parameters is not robust in subjects with Hydrochlorothiazide (P Leren *et al*[9]. Eriksson *et al* studied the effect of the drug Hydrochlorothiazide on insulin resistance and visceral andhepatic fat accumulation and found out that Hydrochlorothiazide was associated with visceral fat redistribution and increased Liver fat accumulation. A blood Lipid-lipoprotein elevating effect of the diuretics Hydrochlorothiazide and Chlorthalidone in mildly hypertensive men has been established by a cross-over, randomized controlled trial, confirming previous clinical observations. Compared to baseline, plasma Total Cholesterol increased 6% and 8% and triglycerides 17% and 15% under treatment with Hydrochlorothiazide and Chlorthalidone, respectively[11].

Conclusion :

To conclude, Chlorthalidone was found to be a relatively more potent anti-hypertensive on both Systolic and Diastolic Blood Pressure when compared with Hydrochlorothiazide. It is more importantly so, as Hydrochlorothiazide is conventialy more popular in this Part of the World as compared to Chlorthalidone. Both these drugs failed to show any significant difference in the Lipid Profile and anthropometry in a period of six months.

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