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Full Length Research Paper

An Observational Study to evaluate the behavior of physicians focusing on the preference patterns of ARB/HCTZ combinations containing high dose (25 mg) diuretic for the treatment of hypertension in Saudi Arabia

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The Hypertension Guidelines 2007 ESH/ESC recommend a two drug combination therapy in patients failing blood pressure goal under monotherapy. The objective of this study is to evaluate the preference patterns of ARB/ high dose HCTZ combinations in the treatment of hypertension in patients uncontrolled by at least 4 to 8 weeks full dose ARB monotherapy. This was a prospective, non-interventional study with a sample size 529 recruited from 81 private and institutional sectors from internal medicine or general practice in Saudi Arabia, during January 2011 to January 2014.Patients classified as uncontrolled by previous full-dose ARB-based monotherapy and to whom the treating physician decided to prescribe ARB/HCTZ combination therapy were eligible for inclusion. Blood pressure was measured at baseline and subsequent visits, up to 4 months. Subgroup analysis was performed based on previous treatment, existing risk factors, gender, and age. All statistical tests were performed using two-tailed tests at a 5% level of significance. The mean reduction of systolic and diastolic blood pressure from baseline to last visit for all patients is 28.5 mmHG and 16.42 mmHg, respectively. The subgroup analysis did not reveal any significant effect on the development of the blood pressure. While uncontrolled at baseline, 51.4 % of the patients were classified as controlled under the combination therapy after 4 months. The registry supports the medically well tolerated combination therapy for hypertensive patients with a meaningful effect in blood pressure reduction and further 50 % higher proportion of controlled patients.

Keywords: Hypertension, combination, physician's preference

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List of Abbreviation

ESH, European Society of Hypertension; ESC, European Society of Cardiology; ARB, Angiotensin Receptor Blockers; HCTZ, Hydrochlorothiazide; SFDA, Saudi Food and Drug Administration; PV, Pharmacovigilance; CRF, Case Report Form; CI, Confidence Interval; BMI, Body Maß Index

INTRODUCTION

Globally, the reported prevalence of hypertension in the adult population varies widely (Kearney et al., 2004; Altun et al., 2005) but the overall number of adults with hypertension worldwide is still predicted to increase (Kearney et al., 2004). Unfortunately, despite the availability of effective pharmacological and non-pharmacological treatments for hypertension, and the widespread dissemination of management guidelines and treatment goals, blood pressure control rates are very poor. Physicians have methods to overcome this issue, e.g. by increasing the dose, adding a new drug or switching the therapy to another anti-hypertensive agent. As stated in the 2007 ESH/ESC Hypertension Guidelines, if blood pressure goal is not achieved by full dose monotherapy, a drug combination at full dose is recommended (Altun et al., 2005). Moreover it is recommended in both 2003 and 2007 ESH/ESC Hypertension Guidelines (The Task Force for the Management of Arterial Hypertension of the ESH and ESC, 2007; Giuseppe Mancia and Co-Chairperson, 2007) to initiate therapy with a two drug combination at low dose in hypertensive patients with high/very high cardiovascular risks. Diuretics are one of the most preferred drugs in combination therapy. In combination therapy two dose regimens are available for combination treatment worldwide such as 12.5 mg and 25 mg of hydrochlorothiazide. However, physicians hesitate to treat hypertension aggressively and still prescribe low dose monotherapies as an initiation.

In this registry the preference patterns of ARB / high dose HCTZ combinations in the treatment of hypertension was evaluated. The analysis was performed in patients uncontrolled by at least 4 to 8 weeks full dose ARB monotherapy. The overall aim was to clarify in which kind of patients ARB / high dose HCTZ combinations are preferred in the treatment of hypertension and to evaluate if the preference is related with patient profiles, co-morbidities, cardiovascular risk factors and to evaluate patient tolerability profile.

METHOD

The study was designed as a prospective, national, multicenter, non-interventional on the therapeutic strategy disease registry study. The registry was conducted in Saudi Arabia. The investigators were selected in accordance with geographic distribution from private as well as from institutional sectors from internal medicine or general practice. In total 915 patients were recruited at 81 investigational sites. The registry study was initiated with first patient included in January 2011 and completed in January 2014 with the last patient visit. The duration for the individual patient was 4 months. This study was conducted in compliance with the Guidelines for Good Epidemiological Practice and applicable national law and regulations of Saudi Arabia (International Society for Pharmocoepidemiology, 1996; IEA European Federation, 2004).

Hypertensive patients medically classified as uncontrolled under full dose ARB monotherapy who met inclusion and exclusion criteria were eligible for this registry. At the selected sites, enrolment of patients was done on sequential basis in accordance with defined eligibility criteria.

Inclusion criteria

1. Male or female > 18 years old
2. Patients uncontrolled (SBP>140 mmHg and DBP>90mmHg) by previous full-dose ARB-based monotherapy (treated at least 8 weeks)
3. Patients who will be treated with ARB and HCTZ combination therapy
4. Patients having signed the informed consent prior study entry.

Exclusion criteria

1. Hypersensitivity to active substance or any excipients.
2. Pregnancy – Lactation
3. Renal impairment
4. Refractory hypokalemia, hypercalcemia
5. Hepatic impairment, biliary cirrhosis and cholestasis
6. Patients not treated with ARBs

No replacement strategy was implemented to substitute non- enrolling registry sites.
In total 915 patients were enrolled of which 386 patients were excluded from final study analysis, leading to 529 eligible patients. Exclusion of patients from final analysis was primarily based on the following reasons:

Patients were enrolled on the registry prior to official registry start,
Patients did not receive full dose of ARB monotherapy prior to enrolment,
Patients were already on combination therapy at enrolment,
Patients´ blood pressure (either systolic or diastolic) didn't fall under the protocol definition of "uncontrolled hypertension".

The registry was conducted in accordance with Helsinki Declarations. The registry was conducted in compliance with all international guidelines, national laws and regulations of the country where it was performed, and any applicable guidelines.

All necessary IRB/IEC submissions were performed in accordance with local regulations.IRB approval was obtained from Institutional Review Board, King Saudi University, College of Medicine.

After patient's agreement to participate, an informed consent form was to sign prior to entry to the registry study. For this observational study the physician made the independent decision to initiate ARB / high dose HCTZ combination therapy as part of the routine clinical care. Blood pressure levels, the physicians stepwise approach in change of medical therapy for uncontrolled patients and patient compliance were recorded at start, visit 1 – baseline, visit 2 (after 2 months) and end of the observation period (visit 3 = after 4 months). Adverse events were reported and managed in compliance with applicable regulations (SFDA PV Guideline, version 2.1, 2011) and Good Clinical Practice, using an Adverse Event form included in the CRF and Serious Adverse Event form as stand-alone form provided by the sponsor.

Paper Case Report Forms were used for the collection of data. Six (6%) of the active sites were randomly selected and checked for the CRF entries against the source documents before collection of completed CRF. Data entries were made in the database only after reviewing the case report forms for completeness and consistency. Data queries were generated for any missing data or missing CRF pages. After receiving the query responses from the sites, responses were reviewed and missing data completed prior to query closure. The patient data were reviewed to ensure that patients included in the data analysis set met the study eligibility criteria and conducted the study in compliance with the registry protocol.

The data set for analysis included eligible subjects, considered as those who met the inclusion criteria and did not have any of the exclusion criteria and who had completed the study as per registry protocol. Data were summarized using mean, median, standard deviation with 2-sided 90% CI of the mean and range for continuous parameters and counts and percentages for categorical parameters. All statistical tests were performed using two-tailed tests at a 5% level of significance. Descriptive analytical methods were used to analyze data and calculate the number of patients.

The safety population was defined including any patient enrolled in the study.

Proportion of controlled patients was calculated at 2 and 4 months visits as percentage of hypertensive patients that have reached the systolic blood pressure (SBP) < 140 and diastolic blood pressure (DBP) < 90 mmHg or < 130/80 mmHg for diabetic patients. Any patient with either SBP or DBP above the defined cut-off values was not counted as "controlled" patient. Proportion of uncontrolled patients was calculated at 2 and 4 months visits as percentage of hypertensive patients that didn't reach systolic blood pressure < 140 or diastolic blood < 90 mmHg or < 130/80 mmHg for diabetic patients. Any patient with either SBP or DBP at or above the defined cut-off values was counted as "uncontrolled".

RESULTS

Subjects characteristics

Out of 529 participants, 361 (68.3 %) were male and 159 (30.0 %) were female. For 9 subjects (1.7 %) the sex was not recorded. Age was recorded for all 529 subjects. The mean age is determined as 50.9 years (with a minimum age of 23 years and a maximum age of 90 years). Mean BMI was found to be 31 kg/m2 (95% CI; 21.5, 40.4). BMI was not possible to be calculated in 52 patients either due to missing height or weight. The mean duration of hypertension since first diagnosed is provided in the table 1 below.

Table 1. Mean duration of hypertension at baseline

Count	529
Missing	11
Mean	59,2 months
SD	54,7
Minimum	2 months

Analysis of risk factors and co-morbidities

Out of the total group of subjects, 309 were non-smokers (58.4 %) and 151 were active smokers (28.5 %). 12.3 % (65 subjects) reported a smoking history. No data on smoking habits were obtained from 4 subjects (0.8 %). Almost 40 % (202 subjects - 38.2 %) were diagnosed with Type 2 DM and 12 subjects (2.3 %) with Type 1 DM. The majority of subjects are non-diabetic patients (309 = 58.4 %). Data on diabetic status of subjects is missing from 6 subjects (1.1 %). Dyslipidemia was diagnosed for 311 patients (58.8 %) and salty food as risk factor was identified in 248 patients (46.9 %). Data about other risk factors associated with hypertension such as physiological stress (191/36.1 %) and low exercise level (379/71.6 %) as well as sleep apnoea (379/71.6 %) were determined with medically relevant prevalence rates.

Previous hypertension treatments

The majority of patients (235/44.42%) were initially treated with Irbesartan 300 mg (median dose) as ARB monotherapy, followed by 78 patients (14.74%) treated with Losartan 100mg (median dose) and 55 patients (10.40%) treated with Valsartan 320 mg (median dose). The list of all ARBs taken by the patients before registry enrolment is given below in table 2.

Table 2. Overview of ARB taken by patients prior to registry enrolment

ARB monotherapy	N	%	Median dose
Candesartan	49	9.26	16mg
Candesartan	15	2.84	32 mg
Eposartan	16	3.02	600 mg
Irbesatan	235	44.42	300 mg
Losartan	78	14.74	100 mg
Olmesartan	40	7.56	40 mg
Olmesartan	1	0.19	60 mg
Olmesartan	2	0.38	80 mg
Telmesartan	38	7.18	80 mg
Valsantan	55	10.40	320 mg

Table 3. Mean systolic and diastolic blood pressure from baseline to visit 3

Variables	Baseline visit		Visit 2		Visit 3	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Count	529	529	529	529	529	529
Missing	0	0	2	2	22	22
Mean	158	97.9	137.1*	86.3*	129.5*	81.5*
SD	12.6	5.9	10.9	6.7	8.9	5.4
CI 95%	133.3 182.7	86.3, 109.5	115.6, 158.6	73.3, 99.3	112.1, 146.9	71.0, 91.9
Minimum	140	90	90	60	105	65
Maximum	220	120	180	110	165	100

*p<0.05 using paired t-test

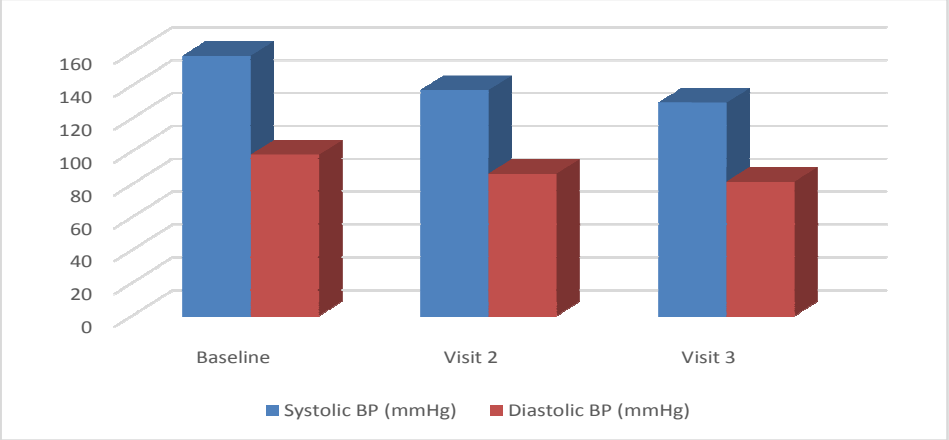

Figure 1. Mean difference in systolic and diastolic blood pressure between patients'

Mean Systolic and Diastolic blood pressure from baseline to registry completion after 4 months

The following table gives an overview about the blood pressure from baseline to visit 3 after 4 months, whereby calculation was done with 95 % confidence interval.

Data on the mean difference in systolic and diastolic blood pressure from baseline to visit 3 is provided in the figure 1.

The mean reduction of systolic and diastolic blood pressure from baseline to visit 3 for all patients is 28.5 mmHG and 16.4 mmHg, respectively which was statistically significant (p<0.05) using paired t-test.

Sub analysis of potential risk factor: gender, diabetes and age

The analysis of parameter values on systolic and diastolic

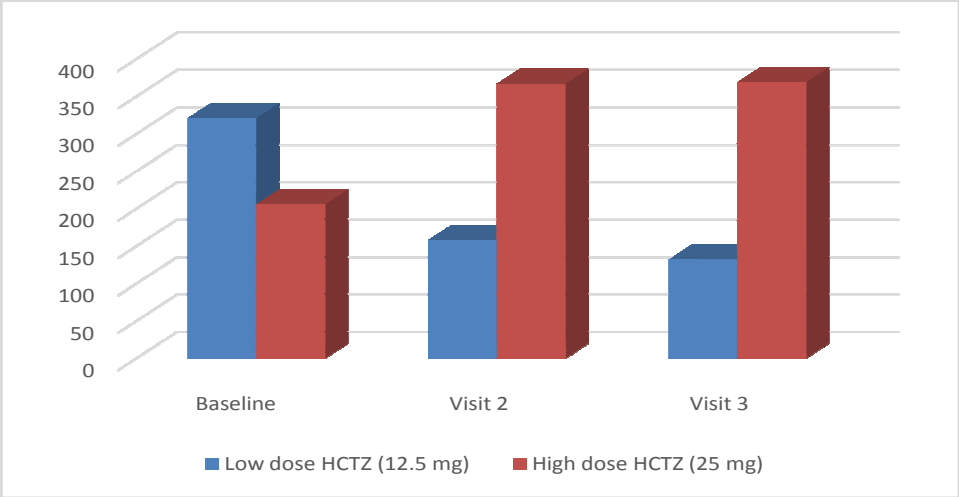

Figure 2. HCTZ Dose levels at baseline visit and subsequent visits

Table 4. Mean systolic and diastolic blood pressure from baseline to visit 3 in higher dose of HCTZ

Variables	Baseline visit		Visit 2		Visit 3	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Count	472	472	472	472	472	472
Mean	159.2	98.1	138.3*	86.8*	129.4*	81.4*
SD	14.5	6.7	11.1	6.8	8.5	5.1

*p<0.05 paired t test

blood pressure in selected subgroup did reveal only very little, non-significant differences between male and female subjects, diabetic and non-diabetic as well as patients below or over 40 years of age.

Primary objective - calculation of controlled and uncontrolled subjects as defined in registry protocol

Among the 529 total eligible patients, 22 patients were further excluded from primary analysis as the SBP and DBP recordings were missing at visit 3. Primary analyses were carried out on 507 patients. The percentage of controlled patients was 26.6 % at visit 2 and increased to 51,5 % at visit 3.

Primary objective - treatment modification at visit 2 and visit 3 with uncontrolled patients

Analysis of prescription patterns of ARB therapies revealed that Irbesartan 150mg/300 mg was found to be the most commonly prescribed ARB (434/81.6 %) at baseline. Treatment modification during visit 1 and visit 2 led to 445 patients at visit 1 (84.2 5) and 423 patients at visit 3 (79,9 %) receiving either 150 mg or 300 mg Irbesartan. Frequency analysis determined Valsartan and Olmesartan as next frequently prescribed ARBs with a proportion of in total 3.2 % and 3.9 %, respectively at visit 3.

Combination therapy with HCTZ was initiated in the majority of patients (321 / 60.7 %) at baseline with 12.5 mg. At visit 2 HCTZ was increased from 12.5 to 25 mg in approximately 30% of patients with 70% of the patients receiving 25 mg dose level. The dose level of HCTZ at visit 3 was not significantly changed from visit 2.

Among patients who had a higher dose of HCTZ, the blood pressure variations were statistically significant ($p<0.05$) from baseline to end of treatment. The following table 4 presents the change in blood pressure from baseline to Visit 3.

The following table 5 provides more detailed information on physicians' decision in regards to dose adjustment for both ARB and HCTZ to achieve the blood pressure goals.

Around 60% of the patients were labelled as controlled at visit 2 and 90% of the patients were labelled as controlled at visit 3.

Data analysed did not indicate any preference in prescription modifications related with patient profiles, co-morbidities, and investigated risk factors. In order to identify the impact of patients' compliance on the registry outcome, data on patients´ compliance were evaluated for visit 2 and visit 3. The majority of patients complied

Table 5. Stepwise approach by physicians to treatment modification at visit 2 and visit 3

Variables	Visit 2		Visit 3	
	N	%	N	%
Total count	529	100	529	100
Missing values	3	0,6	23	4,3
Patient controlled	317	59,9	472	89,2
Prescribed the same fixed combination but with higher dose of HCTZ	138	26,1	22	4,2
Prescribed the same fixed combination but with higher dose of ARB	31	5,9	5	0,9
Prescribed the same fixed combination but with higher dose of both ARB and HCTZ	10	1,9	1	0,2
Switch to another ARB and low dose HCTZ	9	1,7	0	0
Switch to another ARB and high dose HCTZ	16	3	5	0,9
Prescribed the same fixed combination but with lower dose of HCTZ	4	0,8	1	0,2
Prescribed the same fixed combination but with lower dose of ARB	1	0,2	0	0
Prescribed the same fixed combination but with lower dose of both ARB and HCTZ	0	0	0	0

with the registry treatment procedures (96.4 % at visit 2 and 92.6 % at visit 3). Only 17 patients (3.2 %) were classified as non-compliant due to either medication errors and/or patient's negligence.

Safety

During the registry, no Adverse Drug Reactions (ADR) were reported. Solicited AEs were not planned to be collected and unsolicited safety data was not reported by any investigator.

DISCUSSION AND CONCLUSION

A total of 529 patients were enrolled in this registry with an overall number of 507 patients eligible for primary analysis. The registry was conducted at 81 investigational sites in Saudi Arabia, whereby the investigators belonged to institutional as well as the private sector. Only patients who previously were unsuccessfully treated with an ARB monotherapy were included and were prescribed an ARB/HCTZ combination therapy by the treating physician, with either low dose HCTZ (12.5 mg) or a high dose HCTZ (25 mg). Based on the control status of the blood pressure, the treating physician changed the treatment while registry was conducted as medically appropriate by physicians' discretion.

While uncontrolled at baseline, 26.6 % of the patients at visit 2 and 51.4 % at visit 3 were classified as controlled under the combination therapy. On analysis of blood pressure at baseline and subsequent visits, the study showed reduction of 28.5 mmHG and 16.4 mmHg, in Systolic Blood Pressure and Diastolic Blood Pressure respectively, which was a statistically significant change ($p<0.05$).

The analysis of key risk factors (gender, age and diagnosed diabetes) did not reveal any significant effect on the development of the blood pressure during the registry.

The outcome of the registry is in line with up-to-date results on treatment of hypertension with an ARB/HCTZ combination therapy (Greathouse and Weir, 2012) and provides useful information on prescription behaviour and treatment options currently favoured by Saudi Arabic physicians. Although the described registry study was not designed as randomized controlled trial, the outcome of the study gives medically relevant directions for the treatment of hypertension patients in the Saudi Arabia. Limitations to the presented results are mainly linked to the non-controlled and non-randomized, unblinded design of the study. In summary this observational, non-controlled, multi center, prospective registry study conducted in the Saudi Arabia, in patients with uncontrolled hypertension supports the medically well tolerated combination therapy for hypertensive patients with a meaningful effect in blood pressure reduction and further 50 % higher proportion of controlled patients after 4 months of treatment. At the end of this registry almost 70% of the patients were prescribed combination of full dose of ARBs and high dose of hydrochlorothiazide (25mg) which is matching with Eur Heart J 2007; 28: 1462-1536 guideline (3). HCTZ treatment is also associated with a decline of renal function in spite of a lowering blood pressure (Reungjui et al., 2008). However, the current study did not report any unsolicited safety data by any investigator. A study with longer duration would be interesting to conduct, to observe how the benefit shown during the 4-month treatment could be at least maintained if treatment as provided up to visit 3 is pursued and to further investigate changes in prescription patterns by Saudi Arabian physicians based on this registry results.

REFERENCES

Altun B, Arici M, Nergizoglu G, et al (2005). Prevalence, awareness, treatment and control of hypertension in Turkey (the PatenT study) in 2003. J. Hypertens. 23: 1817-1823

Giuseppe Mancia, Co-Chairperson (2007). 2007 Guidelines for the Management of Arterial Hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC); J. Hypertension. 25:1105–1187

Greathouse MK, Weir MR (2012). The role of ARBs alone or with HCTZ in the treatment of hypertension and prevention of cardiovascular and renal complications. Postgrad. Med. 124(2):40-52

IEA European Federation (2004). 'Good Epidemiological Practice (GEP) proper conduct in epidemiology research'.

International Society for Pharmocoepidemiology (1996). 'Guidelines for Good Epidemiology Practices for drug, Device, and Vaccine Research in the United States'.

Kearney PM, Whelton M, Reynolds K, Whelton PK, He J (2004). Worldwide prevalence of hypertension: a systematic review. J. Hypertens. 22: 11 - 19

Reungjui S, Pratipanawatr T, Johnson RJ, Nakagawa T (2008). Do Thiazides Worsen Metabolic Syndrome and Renal Disease? The pivotal roles for Hyperuricemia and Hypokalemia. Curr. Opin. Nephrol. Hypertens. 17(5): 470–476.

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) (2007). 2007 Guidelines for the management of arterial hypertension. Eur. Heart J. 28: 1462–1536