Original Article

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Short Term Safety and Tolerability of a Fixed Dose Combination of Olmesartan, Amlodipine and Hydrochlorothiazide

Internal Medicine Section

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ABSTRACT

Objective: To assess the short term safety and tolerability of a fixed dose combination (FDC) of olmesartan, amlodipine and hydrochlorothiazide (OAH) in real-world clinical setting in India.

Materials and Methods: Physicians were requested to provide eight weeks observational clinical event data of the patients prescribed with FDC of Olmesartan (20/40mg), Amlodipine (5mg) and hydrochlorothiazide (12.5mg) in the prescription event monitoring (PEM) forms. Data on patients' demographics, indication for FDC, concomitant medication and other relevant history was also collected and was analysed with descriptive statistics.

Results: Two hundred thirty eight physicians provided data of 4763 patients. Mean age of the population was 55±7 years and males were 59.3%. The commonest indication for the FDC was uncontrolled hypertension (60.7%). Diabetes and dyslipidemia were present in 37.9% and 35.1% respectively. Concomitant medications included statins (42.3%), oral anti-diabetic (33.7%) and antiplatelet agents (24.7%). Pedal oedema (0.29%) was the most common adverse event (AE) reported followed by headache (0.16%), giddiness (0.15%), light headedness (0.15) and stroke (0.15%). Other less common (0.04%) reported AEs were tiredness, dizziness, gastritis, hypersomnia, hypoglycaemia, lower respiratory tract infection (LRTI), weakness, diarrhea, labyrinthitis, urinary tract infection, hyponatremia and hypotension. Occurrence of AEs was more common in patients with uncontrolled hypertension (60.74%).

Conclusion: The FDC of olmesartan, amlodipine and hydrochlorothiazide prescribed most frequently for patients with uncontrolled hypertension and co-morbidities was found to be safe and well tolerated over a short period of observation.

Keywords: Adverse event, Hypertension, Observational, Prescription event monitoring

INTRODUCTION

Arterial hypertension (HTN) is one of the leading risk factors for cardiovascular (CV) morbidity and mortality. It is an important modifiable risk factor. Blood pressure (BP) reduction has the potential to both reduce CV death and attenuate progression of renal disease [1,2]. Failure to achieve BP goal with monotherapy is common in majority of patients with hypertension [3] particularly those with stage-II hypertension and with co-morbidities, such as diabetes or renal insufficiency. Most patients require two or more antihypertensive agents from complementary classes to achieve BP control [4] and, in several trials, the mean number of agents required to achieve target BP was three or more [5]. One such triple drug fixed dose combination (FDC) of olmesartan, amlodipine and hydrochlorothiazide (OAH) was approved by FDA in 2010 and is being extensively marketed in India. This FDC has been shown to have greater BP reduction compared to the component dual combination [6]. Little is known about safety of this FDC in the Indian hypertensive patients.

Prescription event monitoring (PEM) is a form of 'pharmaco-vigilance' which provides useful information on drug safety signals in the form of 'events' when the drug is prescribed in routine clinical practice. PEM represents 'real world' usage of the drug in general practice. It is helpful in identifying the indications and also provides better assessment of the hazard associated with the new drug or combination [7].

This observational PEM study was conducted to assess short term safety and tolerability of a FDC of OAH in clinical setting in India.

AIM AND OBJECTIVE

The objective of the study was to determine short term safety and tolerability of a FDC of olmesartan 20/40 mg + amlodipine 5 mg + hydrochlorothiazide 12.5 mg when used for the management of hypertension.

MATERIALS AND METHODS

We conducted a non-interventional, observational PEM study at 238 outpatient settings across India between April-July 2013. A prescription event monitoring study booklet was provided to the physicians containing a letter of introduction to the doctor, a study flow chart and PEM case report forms. Physicians involved in management of hypertension were requested to provide the clinical adverse event data of the patients who were prescribed with FDC of OAH for the treatment of hypertension. The decision regarding the choice of drug and dosage was entirely based on the physician's clinical judgment. Data was collected on patient's baseline demographics and the clinical diagnosis. Additional information related to the concurrent medications or any other relevant medical history like diabetes, dyslipidemia, and cerebrovascular disease, active hepatic and renal disease was collected in the PEM forms. Eight weeks follow-up data of each patient was collected. Physicians were requested to record any 'events' that occurred during this observation period in the PEM forms. At the end of the study, all the completed PEM booklets were collected. Data was analysed using descriptive statistics with Microsoft excel 2010.

RESULTS

Demographic characteristics

Data from 4763 patients were available at the end of the observation period. The mean age of the population was 55±7 years. Gender wise, 59.3% (n=2822) were males and 36.9% (n= 1758) were females. Gender was not specified in 3.84% (n= 183) forms [Table/Fig-1].

Comorbidities and Concomitant medications

Type 2 diabetes (37.95%), dyslipidemia (35.08%) and both diabetes with dyslipidemia (15.32%) were common comorbidities.

This is complemented and suggested by common use of oral hypoglycaemic agents (33.67%) and statins (42.28%). Other comorbidities and concomitant medications prescribed are described in [Table/Fig-1].

Dose of FDC prescribed according to HTN category

In the study population, 39.26% (n=1870) patients had newly diagnosed stage II HTN, while 60.74% (n= 2893) patients were having uncontrolled HTN. The details of patients in both the groups and the dose prescribed by the physicians are described in [Table/Fig-2]. Among newly diagnosed patients, 26.64% (n=1269) and 5.56% (n=265) received FDC with olmesartan 20 mg and 40 mg dose respectively whereas in uncontrolled hypertensive patients, 22.84% (n=1088) and 28.66% (n=1365) received FDC with olmesartan 20mg and 40mg dose respectively. Data on the dose of FDC prescribed was not available for 16.29% patients.

SAFETY ANALYSIS

Seventy three adverse events were reported in 1.39% (66/4763) of the study population. The commonest event reported was pedal oedema 0.29% (n=14) followed by headache 0.16% (n=8), giddiness 0.15% (n=7), light headedness 0.08% (n=4), stroke 0.06% (n=3). Other less common (frequency<0.06%) AEs are tiredness, dizziness, gastritis, hypersomnia, hypoglycaemia, lower respiratory tract infections, weakness and hypotension etc. as presented in [Table/Fig-3].

Occurrence of the adverse events was nearly uniform in different patient subgroups except for higher number of giddiness in males (n=6) compared to females (n=1) [Table/Fig-4]. Incidence of the AEs was not different in two genders, in young or old and in patients with different morbidities.

Characteristic	Value	%
Age (Mean ± SD)	55±7	-
Gender		
Males	2822	59.3%
Females	1758	36.9 %
Gender data NA	183	3.84%
Co-morbidities		
Type 2 Diabetes Mellitus (T2DM)	1808	37.95
Dyslipidemia	1671	35.08
T2DM with Dyslipidemia	730	15.32
Cerebrovascular disease	322	6.76
Renal disease	108	2.26
Hepatic disease	76	1.59
Others	813	17.06
Concomitant Medications		
Oral hypoglycaemic agents	1604	33.67
Statins	2014	42.28
Antiplatelet	1179	24.75
Others	790	16.5

[Table/Fig-1]: Baseline characteristics of the patients
NA – Not Available

HTN Category	Total		OAH (20+5+12.5)		OAH (40+5+12.5)		Data NA	
	N	%	N	%	N	%	N	%
Newly Diagnosed (Stage II)	1870	39.26	1269	26.64	265	5.56	336	7.05
Uncontrolled	2893	60.74	1088	22.84	1365	28.66	440	9.24
Total	4763		2357	49.49	1630	34.22	776	16.29

[Table/Fig-2]: FDC dose according to HTN category

Adverse Events (AEs)	n	%
Total number of patients reporting AEs	66/4763	1.39
Total number of AEs	73	-
AEs in Newly Diagnosed HTN (Stage II)	25/66	37.89
AEs in uncontrolled HTN	40/66	60.61
Events occurred		
Pedal oedema	14	0.29
Headache	8	0.16
Giddiness	7	0.15
Light Headedness	4	0.08
Stroke	3	0.06
Tiredness	2	0.04
Dizziness	2	0.04
Gastritis	2	0.04
Hypersomnia	2	0.04
Hypoglycaemia	2	0.04
LRTI	2	0.04
Weakness	2	0.04
Hypotension	2	0.04
Dryness of mouth	1	0.02
Angina	1	0.02
Chest Discomfort	1	0.02
COPD Exacerbation	1	0.02
Diarrhea	1	0.02
Dysgeusia	1	0.02
Fatigue	1	0.02
Gastric Bloating	1	0.02
Hyponatremia	1	0.02
Hypovolemia	1	0.02
Itching	1	0.02
Labyrinthitis	1	0.02
LBBB	1	0.02
Loose Motion	1	0.02
LV dysfunction	1	0.02
Muscle Cramps	1	0.02
Myalgia	1	0.02
Offensive smell	1	0.02
Palpitation	1	0.02
Postural hypotension	1	0.02
UTI	1	0.02

[Table/Fig-3]: Frequency of occurrence of events
LRTI-lower respiratory tract infection, COPD-Chronic obstructive pulmonary disease, LBBB-Left bundle branch block, UTI-Urinary tract infection

DISCUSSION

In this prescription-event monitoring study, we assessed the safety profile and occurrence of any 'events' with the use of FDC of olmesartan (20/40mg), amlodipine (5mg) and hydrochlorothiazide (12.5 mg) when used for the management of hypertension in real world clinical situation. Although similar studies with FDC of OAH have been conducted, this is probably the largest safety evaluation for this FDC in Indian scenario [8,9].

Mean age of the study population was 55 years with a predominant male population suggesting middle-aged males are at higher risk of HTN needing multiple drug therapy. In clinical settings, the common indication for prescribing the FDC was uncontrolled hypertension (60.7%). It was observed that physicians preferred this three drug FDC in newly diagnosed in Stage II (DBP≥ 100 mmHg and SBP ≥160 mmHg) hypertensives, as recommended by Joint National Committee (JNC) 8 panel [10]. A lower strength of FDC was preferred

Adverse Events* (frequency > 2)	Subgroups (n)									
	All [n (%)]	Gender		Age (Years)		Co-morbidities				
		M	F	< 60	≥ 60	DM	Dyslip	DM + Dyslip	CbVD	Renal disease
Pedal oedema	14 (0.29)	6	8	9	5	4	4	3	3	-
Headache	8 (0.16)	5	3	2	6	4	5	2	-	-
Giddiness	7 (0.15)	6	1	4	2	4	3	2	-	1
Light Headedness	4 (0.08)	2	2	3	1	2	1	-	-	-
Stroke	3 (0.06)	3	-	3	-	2	1	1	3	-
Total AEs	36	22	14	21	14	16	14	8	6	1

[Table/Fig-4]: Major adverse events (> 2 in number of events) among different patient subgroups
DM – Type 2 Diabetes mellitus, Dyslip – Dyslipidemia, CbVD – Cerebrovascular disease

in newly diagnosed stage II hypertensives whereas a higher strength of olmesartan (40 mg) was preferred in uncontrolled hypertensive patients. This suggests a rational approach in management of HTN by the physicians.

From total study population, 73 AEs were reported in 66 patients during 8 weeks period. The most common adverse event reported in this study was pedal oedema (0.29%). Similarly, pedal oedema (7.7%) is the most common AE identified and reported in the United States Food and Drugs Administration (USFDA) approved drug label [11]. Peripheral oedema is a common side effect with amlodipine reported to occur in 9-34 % patients, and is ameliorated with use of olmesartan which reduces the post capillary resistance [12].

Other common events were headache and giddiness. Headache (0.16 %) is a common reported event with the use of amlodipine (8.3%) [13] and also with olmesartan (0.5%). Other less common events reported were gastrointestinal symptoms like gastritis, diarrhea, chest pain, myalgia, itching, and hypersomnia. These events seen in this study are in line with the available information in the product literature of all the individual drugs [11,13].

New onset stroke was reported in three patients in the study population. Follow up data of these patients was not available. Concerns have been raised regarding safety of olmesartan, when ROADMAP [14] (The Randomized Olmesartan and Diabetes Micro albuminuria Prevention) and ORIENT [15] (Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial) trials showed a higher incidence of cardiovascular deaths (heart attack, sudden death, or stroke) in patients taking olmesartan as compared to placebo. After reviewing the results from these trials, FDA has determined that the benefits of olmesartan use continue to outweigh its potential risks when used for the treatment of patients with hypertension [16]. Hyponatremia and hypotension can be attributed to presence of hydrochlorothiazide component [17].

Events like stroke, labyrinthitis, urinary tract infection, were not reported in earlier studies. The other reported events in literature on the drug components were back pain, rise in creatinine phosphokinase level, haematuria, hyperglycaemia, hyperlipidemia, hypertriglyceridemia, vertigo, and tachycardia. However, no patients reported any of these in our study.

Diabetes and dyslipidemia in patients with hypertension were a common occurrence, suggesting a higher prevalence of diabetes and dyslipidemia in hypertensive population. Hence the use of statins and hypoglycaemic agents along with the FDC was high in the study population. A small proportion of patients received three concomitant drugs along with this FDC, i.e. antiplatelet, hypoglycaemic and statins. It is also possible that the physicians prefer to use this triple drug combination more often in diabetic subjects.

STRENGTHS AND LIMITATIONS

There was no selection bias as this was a real-world observational study with no inclusion/exclusion criterion. The study methodology ensured that the treating physicians' decision was not influenced. The study is representative of Indian patients as the samples were recruited across the country. A disadvantage of the method is that it relies on practicing physicians for returning completed forms. Under reporting of events by the physicians is possible. Bias caused by this factor or inaccurate reporting by the physicians cannot be excluded. It does appear that incidence of adverse events is lower when compared to the previous such studies. It could partially be due to (a) short duration of follow-up, (b) majority of patients were already on similar drugs, (c) better and more judicious use of the combination.

CONCLUSION

This PEM study for the first time evaluated a safety profile in Indian patients receiving a fixed dose combination of OAH. The frequency of individual adverse events reported in this study did not exceed the frequency in the summary of product characteristics of individual drug components. The FDC containing a combination of olmesartan, amlodipine and hydrochlorothiazide was found to be safe and well-tolerated upto 8 weeks. Long term safety analysis can provide more evidence on rare adverse events that were observed in our study.

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