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Prevalence Of ARB and Ace Inhibitors Induced Hyponatremia Among Hospitalized Patients

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Abstract

Introduction: Hyponatremia is defined as a serum sodium concentration of less than 135mmol/L and associated with disease conditions or as an adverse effect of certain drugs. Due to the increasing poly-pharmacy and an aging population, the prevalence of drug-induced hyponatremia is likely to increase. Among the drug-induced hyponatremia, Angiotensin-Converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blockers (ARB) are found to be the most important. **Method:** Our study was a descriptive cross-sectional study conducted among 150 subjects in the medicine department of Believers Church Medical Hospital (BCMCH), Thiruvalla for 6 months. **Result:** Among 150 patients, 50 patients developed ARB and ACEI Induced hyponatremia. **Conclusion:** Hyponatremia was found to be associated with nearly 33% of patients taking ACEI and ARB, this study revealed that monitoring of serum sodium levels in the patients with ACEI and ARB administration will help to elude unexpected adverse reactions.

Keywords: Hyponatremia; Angiotensin Converting Enzyme Inhibitor (ACEI); Angiotensin Receptor Blockers (ARB); Drug induced; Sodium.

INTRODUCTION

Hyponatremia is the most common electrolyte abnormality in hospitalized patients. (1) and is defined as a serum sodium concentration of less than 135mmol/L.(1,2,3) and most common electrolyte disturbance seen in clinical practice(2) and may be associated with low, normal (275 to 290 mmol/kg), or high osmolality. (4) Hyponatremia may be associated with disease conditions or as an adverse effect of certain drugs. (4) Angiotensin-Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor Blockers (ARB) are drugs that have been commonly prescribed for the treatment of hypertension and cardiac diseases. Hyponatremia may develop occasionally in the course of treatment with drugs used in everyday clinical practice. Drugs have been reported to account for 30% of cases of hyponatremia. The rate of prescribing ACE Inhibitors is around 13.5% and that of AT1 receptor antagonists is 24% in major cities of India. (1)

ACEI and ARB's have also been reported to down-regulate the sodium channel and renin expression in renal tubules. These effects would act to suppress sodium re-absorption via the sodium channel and neutralizes the mechanism that would elevate blood pressure in response to increased salt intake. ARB has been reported to inhibit the vasoconstricting mechanism and aldosterone secreting effects of

angiotensin II leading to decreased renal tubular sodium reabsorption. Clinical manifestations of hyponatremia are primarily neurologic especially in acute hyponatremia and chronic hyponatremia patients may appear asymptomatic. Physicians may not always provide proper attention on time to undesirable drug-induced hyponatremia. Awareness of this less common adverse effect of these drugs on serum sodium levels is of great importance for prevention.

Hence, this study aims to determine the prevalence of hyponatremia in patients on ACEI and ARB.

MATERIALS AND METHODS

Study design: Descriptive Cross-Sectional study

Study site:

The study was conducted at Believers Church Medical Hospital (BCMCH), Thiruvalla on the topic of ―Prevalence of ARB and ACEI induced hyponatremia among hospitalized patients.

Study duration:

Six months (November 2019 to April 2020).

Sample size:

The sample size of 150 patients.

The statistical formula for calculating sample size:

z2*p(1-p)

e2

1+ (Z2*p(1-p)

e2N

Where,

P=Standard deviation

N = Population size

E = Margin of error

Z = 95% Confidence interval of Z

Assuming the expected prevalence of hyponatremia to be 48% as per prior studies and precision to be 10% and level of significance to be 0.05, the estimated minimum sample size is 96.

Study approval:

The study was approved by the Institutional Review Board of Believers Church Medical College Hospital, Thiruvalla.

Study criteria:

The study will be carried out by considering the following criteria:

Inclusion criteria:

IP patients on treatment with ARB and ACEI with Sodium level<135.

Exclusion criteria:

1. Patient with known renal failure
2. Malignancy
3. CCF
4. Liver cirrhosis

Source of data:

- A structured data collection proforma was used for the collection of data.
- Data were collected from medical records and Patient drug charts.
- Serum sodium levels were taken from the lab reports

Study procedure:

The prevalence of hyponatremia was analyzed through a descriptive study conducted in IP patients of the medicine department. The medical records, patient drug charts, and laboratory reports were analyzed by using the record review method. The medical records with incomplete information on drugs and laboratory reports were excluded from data collection.

Statistical method:

The data was entered in Microsoft Excel-2020 version. Results were analyzed as tabular form and percentages (Descriptive analysis).

RESULTS

We studied a total of 150 hypertensive patients who were on ARB and ACEI. Out of the 50 patients (33.3%) had hyponatremia. The maximum no. of patients (77) were in the age group of 61-70 and the prevalence of hyponatremia in this group was 27%. The prevalence of hyponatremia was higher in the 71-80 age group (47%). There were only 22 subjects above the age of 81years and prevalence in this group was 22.7% (Table1).

Volume 4, Issue 4; July-August 2021; Page No 691-699

Among the total patient studied, there were 65 males out of which 16 (24.6%) had hyponatremia. There were 85 female patients out of 34 (40%) who had hyponatremia (Table2). The subjects with hyponatremia based on social history. Two patients of the total had a history of both alcohol and smoking. It was observed that smoking (6%) and alcohol (2%) were not prominent risk factors of hyponatremia (Table3).

A total of 150 subjects, 18 on ACEI and 132 on ARB. Among 150 subjects, 50 patients had hyponatremia. The prevalence of hyponatremia was higher in patients who were taking ARBs than those who were taking ACEIs. The highest prevalence of hyponatremia was observed in patients on Olmesartan followed by Losartan and Telmisartan (Table 4).

Subjects with hyponatremia are classified into 3 different stages based on their severity as Mild, Moderate, and Severe. The sodium level between 130-134meq/l is considered as mild and the level beteen125-129meq/l is termed as moderate and less than 125meq/l as severe. Among the 50 hyponatremic patients, 4% of patients had mild hyponatremia. All of the patients were on ARBS. 38% of patients had moderate hyponatremia and 58% had severe hyponatremia (Table 5).

The most common presenting clinical features were fatigue/tiredness (36%) followed by vomiting (26%), nausea (Table 6).

All patients with hyponatremia had one or more co-morbidities and the prevalence of hyponatremia was more among those with DM when compared with other co-morbidities (Table 7).

The management of hyponatremia in those subjects. Out of the 50 patients with hyponatremia, 72% were managed by the withdrawal of drugs, and 28% were managed by altering the drugs. Among the drugs prescribed ARB (92%) and ACEI (8%) were withdrawn. ARBs were altered with CCBs (Cilnidipine were 86% and Amlodipine ere 14%)[Table8].

DISCUSSION

Hyponatremia may occur due to excess amount fluid compared to the normal level of sodium or due to depletion of both sodium and body fluid. The symptoms include nausea, malaise, and lethargy decreased level of consciousness, headache, seizures, and coma. When there are very low serum sodium levels (<115 meq/L), it can even lead to intracerebral osmotic fluid shifts and brain edema which may become fatal. (1)

With increasing polypharmacy and an aging population, the prevalence of drug-induced hyponatremia is likely to increase. (2) It is often considered that there is no effect of ACEI and ARB on serum sodium levels. However, in recent past years, there are few case reports indicate the incidence of hyponatremia due to ACEI and ARB administration. (1,5,6,7,8)

ACE inhibitors in antihypertensive doses may block the conversion of angiotensin I to angiotensin II in the peripheral circulation but not in the brain. Increased circulating angiotensin I enter the brain and is converted to angiotensin II, which may stimulate thirst and release of ADH from the hypothalamus, eventually leading to hyponatremia. (2) Incidence of hyponatremia was high in the age group 56-75 years compared to the lower age groups (44-55 years) in a study. (1 2) Here it has been reported that more in the age groups 71-80.

Another study on hyponatremia by ACEI had reported a higher susceptibility in males. (2) However, the present study results indicate higher susceptibility of females compared to males. The differences in pharmacokinetics between women and men make women, in general, more susceptible to dose-dependent ADR. The different effects of sex hormones on the renin-angiotensin-aldosterone system (RAAS) are the reason for the development of hyponatremia in females. Sex hormones, such as exogenous and endogenous estrogens and androgens, interact with the RAAS in opposite ways, with estrogens downregulating and androgens up-regulating RAAS. (9)

The prevalence of hyponatremia was significantly higher in females and increased with age. The drugs prescribed for the present study group patients include enalapril, ramipril, telmisartan, valsartan and losartan, and Olmesartan. The incidence of hyponatremia was found to be higher with Olmesartan. Hyponatremia prevalence did not significantly vary with alcohol consumption or any other social habits. (10) But In another study by Cory M. Jenks titled Hyponatremia Secondary to Lisinopril is a Veteran Patient reported

Volume 4, Issue 4; July-August 2021; Page No 691-699

that beer potomania is a contributing factor to Hyponatremia.

LIMITATIONS

- The susceptibility of individuals to develop hyponatremia and the type of drug involved in producing hyponatremia may have a genetic disposition. This could be the cause for the diversity observed in the present and previous studies.
- Further exploration on this aspect requires studies with larger sample sizes to through lighter on hyponatremia induced by these drugs. Time is also another factor.
- Only In patients from the General Medicine department are taken for the study.

CONCLUSION

From this study, we were able to find out the prevalence of ARB and ACEI induced hyponatremia among hospitalized patients. Hyponatremia was found to be associated with nearly 33% of patients taking ACEI and ARB out of the 150 patients. It was reported commonly among the elderly population mostly between 70-80 yrs. of age and reported more in female patients. According to certain studies alcohol (beer potomania) is considered to be a risk factor for Hyponatremia. Though Olmesartan showed a higher incidence of hyponatremia compared to other drugs included in the study, studies with a larger sample size are required to confirm the results. The present study emphasizes the need for monitoring of serum sodium levels in patients on ACEI and ARB administration to elude unexpected adverse reactions.

Tables

Table 1: DISTRIBUTION OF AGE GROUP

Sl.No:	Age group	Total no. of patients	Subjects with hyponatremia	Percentage (%)
1	61-70	77	21	42
2	71-80	51	24	48
3	81-90	22	5	10
	Total	150	50	100

Table 2: DISTRIBUTION OF SUBJECTS ACCORDING TO GENDER

Sl.No:	Gender	Subjects with hyponatremia	Percentage (%)
1	Male (n=65)	16	32
2	Female(n=85)	34	68
	Total	50	100

Volume 4, Issue 4; July-August 2021; Page No 691-699

Table 3: DISTRIBUTION OF SOCIAL HISTORY

		Subjects with hyponatremia	
Sl. No:	Social history	Frequency	Percentage (%)
1	Alcohol (n=10)	1	2
2	Smoking (n=20)	3	6
3	Nil (n=120)	46	92
	Total	50	100

Table 4: OCCURENCE OF HYPONATREMIA ACCORDING TO DRUGS PRESCRIBED

Sl. No:	Class	Drugs	Total no. of subjects	Subjects with hyponatremia (n=50)	Percentage (%)
+1	ARB	Losartan	55	22	40
		Olmesartan	14	6	42.85
		Telmisartan	61	19	31.14
		Valsartan	2	0	0
		Total	132	47	35.6
2	ACEI	Enalapril	8	2	25
		Ramipril	10	1	10
		Total	18	3	16.6

Volume 4, Issue 4; July-August 2021; Page No 691-699

Table 5: DISTRIBUTION OF SEVERITY OF HYPONATREMIA

Class	Stages	Range(meq/l)	Frequency	Percentage (%)
ARB	Mild	130-134	2	4
ACE and ARB	Moderate	125-129	19	38
ACE and ARB	Severe	Less than 125	29	58

Table 6: PRESENTING SYMPTOMS IN PATIENTS WITH HYPONATREMIA

Drugs Class	Clinical features	Frequency	Percentage (%)
ARB	Nausea	8	16
	Vomiting	13	26
	Fatigue/Tiredness	18	36
	Drowsiness	4	8
	History of fall	4	8
	Giddiness/Loss of balance	4	8

Table 7: DISTRIBUTION OF COMORBIDITIES SUBJECTS WITH HYPONATREMIA

Sl. No	Co morbidities	Frequency	Percentage (%)
1	COPD	6	12
2	DM	27	54
3	Thyroid disorder	7	14
4	Bronchial Asthma	10	20

Volume 4, Issue 4; July-August 2021; Page No 691-699

	Total	50	100

Table 8: DISTRIBUTION OF MANAGEMENT IN HYPONATREMIA PATIENTS

Sl. No:	Management	Frequency	Percentage (%)
1	Drug withdrawn	36	72
2	Drug altered	14	28
	Total	50	100

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Volume 4, Issue 4; July-August 2021; Page No 691-699

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Volume 4, Issue 4; July-August 2021; Page No 691-699