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Original Research Article

Hyponatremia induced by angiotensin converting enzyme inhibitors

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ABSTRACT

Background: Hyponatraemia is commonly associated with disease conditions or as an adverse effect of certain drugs. Angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blockers are drugs that have been commonly prescribed for the treatment of hypertension and cardiac diseases. It has become important to evaluate and investigate the incidence of hyponatremia on consumption of these drugs. The study aims to observe the incidence of the adverse drug reaction-hyponatraemia in hypertensive patients on ACEI therapy.
Methods: The patient's data was collected using proforma following which they were randomized into three groups receiving enalapril, ramipril and captipril. Serum sodium levels were assayed by direct ISE method. Statistical analysis of data was performed using SPSS version 21.0. Chi-square test was used to compare occurrence of hyponatremia in the patients on ACEI. $P<0.5$ was considered as statistically significant.
Results: Among all, 26 (52%) of the study population administered with ACEI developed hyponatremia. Predisposition to develop hyponatremia was high in males compared to females. The study also revealed that Enalapril had a higher association with hyponatremia compared to other drugs.
Conclusions: Hyponatremia was induced in 52% of patients taking ACEI. This study revealed that monitoring of serum sodium levels in the patients with ACEI administration will help to prevent unexpected adverse reactions like hyponatremia.

Keywords: Angiotensin converting enzyme inhibitors, Hyponatremia, Adverse drug reactions

INTRODUCTION

The class of drugs called angiotensin converting enzyme (ACE) inhibitors, as the class name suggests, reduce the activity of angiotensin converting enzyme. ACE converts angiotensin I produced by the body to angiotensin II in the blood. Angiotensin II is a very potent chemical that causes the muscles surrounding blood vessels to contract and narrow the blood vessels. Narrowing of blood vessels increases the pressure within the blood vessels and may lead to high blood pressure (hypertension).[1] By reducing the activity of ACE, ACE inhibitors decrease the formation of angiotensin II which leads to widening (dilation) of blood vessels, and thereby reduces blood pressure. By lowering blood pressure against which the heart must pump, the amount of work that the heart must do is reduced. ACE inhibitors also reduce blood pressure in the kidneys, slowing the progression of kidney disease due to high blood pressure or diabetes.[2,3] Hyponatremia is defined as a serum sodium concentration below 135 mmol/l and may be associated with low, normal (275 to 290 mmol/kg) or high osmolality.[4] Clinical severity is dependent both on the magnitude of the hyponatremia and the rate at which the serum sodium level has declined. When the decrease in serum sodium is marked (≤125 mmol/l) or acute (occurring over <48 h), serious neurological complications can ensue as a result of cerebral oedema. Headache, nausea, vomiting, muscle

cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death. Diagnosis is based on a detailed clinical history and physical examination, serum and urinary sodium and plasma osmolality.[5-7] Hyponatraemia is commonly associated with disease conditions or as an adverse effect of certain drugs. With increasing polypharmacy and an ageing population, the prevalence of drug-induced hyponatraemia is likely to increase.[8] Most patients with drug-induced hyponatraemia are asymptomatic and the diagnosis is made incidentally following routine blood tests.[9] 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. It has become important to evaluate and investigate the incidence of hyponatremia on consumption of these drugs.

METHODS

Place of study

This study was placed at Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Telangana, India.

Type of study

This was a cross-sectional study.

Sample collection

Sample size was 50.

Sampling methods: Consecutive sampling.

Inclusion criteria

Patients above 18 years, both sex, having ACEI for minimum of one month were included in the study.

Exclusion criteria

Patients with known renal failure, history of diarrhoea during past one week and intake of additional drugs that have been known to cause hyponatremia were excluded from the study.

Statistical methods

Statistical analysis of data was performed using SPSS version 21.0. Chi-square test was used to compare occurrence of hyponatremia in the patients on ACEI. P<0.5 was considered as statistically significant.

Serum sodium levels were assayed in patients taking ACEI and ARB; 50 patients were recruited. The patient's age, sex, drug dosage, frequency of the drug administration was collected using a proforma. Statistical analysis of data was performed using SPSS version 21.0.

RESULTS

Incidence of hyponatremia

Among all, 52% (26) of the study population administered with ACEI developed hyponatremia. Predisposition to develop hyponatremia was high in males (70%) compared to females (25%). Incidence of hypoanatremia was more (60.7%) in the older age group (56-75 years) compared to the 45-55 years age group.

Table 1: Incidence of hyponatremia.

Variable	Total no. of subjects		Subjects who developed hyponatremia	
	N (%)	Mean sodium level (mEq/l)	N (%)	Mean sodium level (mEq/l)
Gender				
Male	30 (60)	133.1	21 (70)	129.6
Female	20 (40)	135.8	5 (25)	130.9
Age (in years)				
45-55	22 (44)	135.4	8 (36)	130.2
55-65	14 (28)	132.8	9 (65)	130.5
>65	14 (28)	135.2	8 (57)	129.6
Total	50 (100)	136.0	26 (52)	130.3

Hyponatremia induced by individual drugs

10 (63%) subjects who were prescribed enalapril developed hyponatremia, whereas 14 (50%) and 1 (17%) subjects who were prescribed ramipril and captopril respectively developed hyponatremia.

Table 2: Hyponatremia induced by individual drugs.

Drug	Total no. of subjects	Subjects who developed hyponatremia (%)
Enalapril	16	10 (63)
Ramipril	28	14 (50)
Captipril	6	1 (17)

DISCUSSION

Drug induced hyponatraemia is commonly associated with diuretics, selective serotonin reuptake inhibitors and antiepileptics. With increasing polypharmacy and an aging population, the prevalence of drug induced hyponatraemia is likely to increase. Angiotensin converting enzyme inhibitors are a group of vasodilators which are frequently used for the treatment of hypertension and congestive cardiac failure. They have been found to cause significant hyponatraemia

occasionally, alone or in combination with diuretics or salt restriction. Approximately 20 cases of severe hyponatraemia with ACE inhibitors have been reported in literature. ACE inhibitors in antihypertensive doses may block conversion of angiotensin I to angiotensin II in the peripheral circulation but not in the brain. Increased circulating angiotensin I enters the brain and is converted to angiotensin II, which may stimulate thirst and release of ADH from the hypothalamus, eventually leading to hyponatraemia. The present study revealed the occurrence of hyponatremia in 52% of the participants on ACEI (Table 1). This finding coincides with more incidence of hyponatremia with the case reports on ACEI induced hyponatremia.[10] A previous study on losartan had reported higher susceptibility of females to hyponatremia compared to men.[11] However, the present study results indicate higher susceptibility of males compared to females. Incidence of hyponatremia was high in the age group 56-75 years compared to the lower age groups (44-55 years). However, the magnitude of serum sodium lowering was found to be higher in patients above 66 years of age. These results coincide with those of similar studies.[12,13] Assessment and management of a patient with hyponatraemia depends on the clinical status and the likelihood that one or more drugs are responsible. Most hyponatraemic patients would be asymptomatic. Patients with moderate to severe hyponatraemia may present with symptoms like anorexia, nausea, restlessness, muscle weakness, spasm or cramps, confusion, irritability, convulsions and coma. Alternative explanations for these clinical features should always be considered. Conditions which may be responsible for hyponatraemia like cardiac, liver and renal failure should be ruled out.[14] A careful history, examination and clinical assessment of fluid status are needed to exclude non drug causes of hyponatraemia. Raised blood sugar or urea level, pseudohyponatraemia due to hypertriglyceridaemia and paraproteinaemia and other occult co-morbidities like hypothyroidism and hypoadrenalism should be excluded.[15] Syndrome of inappropriate anti diuretic harmone due to some malignancy or central nervous system lesion should also be looked for. In mild to moderate cases of ACE inhibitors induced hyponatraemia or drug induced hyponatraemia with a normovolaemic fluid status clinically, ceasing the offending drug and gentle fluid restriction would improve serum sodium levels gradually within a week.[16,17] In an acutely unwell patient due to severe drug induced hyponatraemia, severe fluid restriction or infusion of hypertonic saline may be required. ACE inhibitors have some potassium retaining properties but serum potassium level usually remains within normal limits when an ACE inhibitor is used alone.[18,19] Patients may show hypokalaemia if thiazide or loop diuretics are used concomitantly with ACE inhibitors.

CONCLUSION

Among all, 26 (52%) of the study population administered with ACEI developed hyponatremia. This study revealed that monitoring of serum sodium levels in the patients with ACEI administration will help to prevent unexpected adverse reactions like hyponatremia.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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