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Original Article

Hydrochlorothiazide and Chlorthalidone Induced Hyponatremia – A Comparative Analysis for Concern

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Abstract
Thiazide diuretics like hydrochlorothiazide (HCTZ) and chlorthalidone (CT) are commonly used pharmacol-ogical agents for the treatment of hypertension preferably in elderly patients. Previously we ignored risk of hyponatremia following diuretics therapy but much more attention paid to prevent hypokalemia. In this study we are giving more attention to the fact that hyponatremia is developed after the use of low dose of HCTZ & CT in hypertensive elderly patient. We reviewed the list of hypertensive patients hospitalized in Midnapore Medical College for hyponatremia from January 2015 to December 2015. We identified 40 (19M/21F) hypertensive patients (mean age 66±9.4yrs) hospitalized because of hyponatremia due to diuretics (HCTZ & CT). Twenty for each group (20HCTZ group & 20 CT group). Across all ages, the OR(Odds Ratio) for severe hyponatremia in HCTZ group vs CT group was 10.2 (95% CI: 1.12 -93.35).The OR for hyponatremia in patients of both Groups male vs female was insignificant. The OR for hyponatremia in patients of both sexes older than 65years vs those younger than 65 years was 1.5 (95% CI:0.84- 5.44). In this study we observed , all patients was received combined antihypertensive HCTZ with ARB or CCB , dose of HCTZ was 12.5mg and CT with ARB , dose of CT was 6.25mg. No dose variation was seen in diuretics.Elderly patients are likely to be at particularly high risk. In such cases diuretic use should be associated with close monitoring of sodium levels.
Keyword: *Hydrochlorothiazide, Chlorthalidone, hyponatremia, elderly.*

Introduction

Diuretics induced hyponatremia is commonly observed in clinical practice. Its use gradually has increased after guidelines (JNC-7) recommending thiazides as first treatment of essential hypertension. Much attention has been paid diuretics induced hypokalemia, whereas other metabolic alterations such hyponatremia, hyperur-ecemia, insulin resistant, hypercalcemia and hypercholesterolemia are paid less attention.

Recently chlorthalidone (CT) is intensely promoted to be used as potent antihypertensive with minimum side effects and is well tolerated over hydrochlorthiazide (HCTZ). Hyponatremia is defined as if Na <135 mg/dl in serum. But our study showed reverse scenario of chlorthalidone.

Material &Methods

This retrospective observational unicentric study was carried out at Medicine Indoor of Midnapore Medical College in West Bengal, a rural based tertiary care Hospital and it was conducted for one year extending from January to December 2015. Patients who receiving diuretic (HCTZ & CT) treatment for hypertension were Included in this study. Patients who had other probable causes of hyponatremia were excluded from this study. We recorded the following parameters for all patients with HCTZ & CT induced hyponatremia: name, age, sex, drugs used, dose & duration of drugs used, associated diseases clinical presentation and laboratory findings on admission. All the patients were known hypertensives on treatment with either HCTZ (12.5mg) or CT (6.25mg) in addition to ACEI/ARBS or CCBS. Forty patients were included in this study. All patients were monitored in either Indoor or HDU or ICU of the medicine ward for BP and hyponatremia correction. All patients were underwent routine clinical examination and laboratory investigations in addition to do plain CT scan brain to rule out any structural damage. HCTZ and CT were discontinued and patients received either extra salt in diet or 3% Nacl infusion for hyponatremia correction.

Observations

We focus on 40 hypertensive patients with diuretic induced hyponatremia by excluding other possible causes of hyponatremia out of 358 patients in this periods. Patients' characteristics detailed in table 1.

Table 1: Patients' Data

	Mean ± SD	Range
No. of patients	40	
Gender(M/F)	19/21	
Age(years)	70±9.4	45-90
Patients ≥65years	29	
SBP(mm Hg)	168± 36	150- 230
Serum Na(mmol/L)	118±7.5	(100 – 132)
Serum K(mmol/L)	3.6 ±0.5	(2.8-4.4)
Serum osmolarity	252±12	(220-254)
SerumUrea(mg/dl)	24±16	(20-40)
Serum Creatinine (mg/dl)	0.8±0.3	(0.5-1.2)
Urine Na (mmol/L)	96±46	(18-186)

SD=Standard Deviation, M =Male , F = Female, SBP = systolic blood pressure.

Across all ages, the OR (Odds Ratio) for severe hyponatremia in HCTZ group vs CT group was 10.2 (95% CI: 1.12 -93.35).The OR for hyponatremia in patients of both Groups male vs female was insignificant. The OR for hyponatremia in patients of both sexes older than 65years vs those younger than 65 years was 1.5 (95% CI:0.84- 5.44). In this study we observed , all patients was received combined antihypertensive HCTZ with ARB or CCB, dose of HCTZ was 12.5mg and CT with ARB, dose of CT was 6.25mg. No dose variation was seen in diuretics. Duration of diuretic treatment prior to the development of hyponatremia was clearly reported in 32 patients of 40. Hyponatremia was diagnosed within 6 months and more than 6 months of treatment in 60% (majority were older than 65years), 40% respectively. We observed 7

patients older than 75 years, hyponatremia was developed within 15 days of treatment. Those who developed hyponatremia shortly after initiation of therapy had similar characteristics to those who developed it after 6th months (p>0.05).

Table 2: male & female No. & percent

Sex	Hydrochlorthiazide (n=20)with percent	Chlorthalidone(n=20) with percent
Male	8 (40%)	11(55%)
Female	12 (60%)	9 (45%)

Figure 1: male & female percent

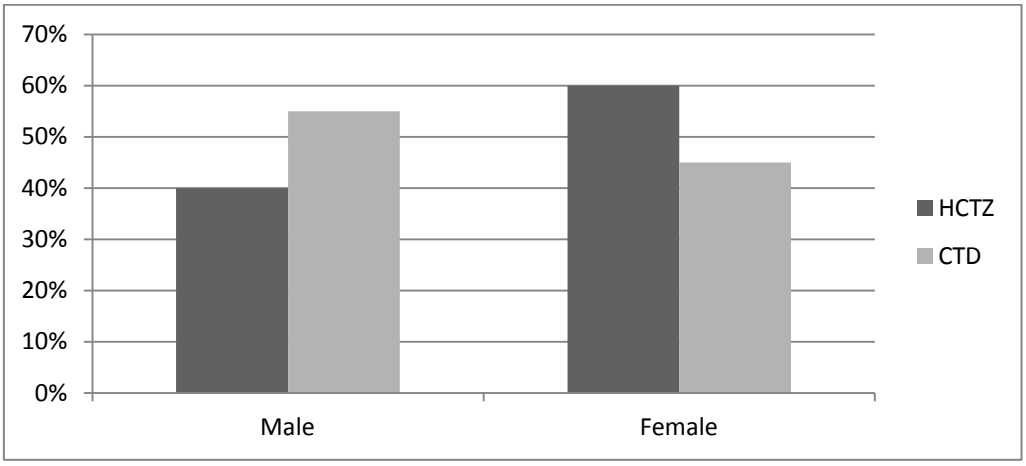

Table 3 : Male patients age wise distribution with No. & percent

Male with age in years	HCTZ(n=8) with percent	CTD(n=11)with percent
45-54	1(12.5%)	0
55-64	2(25%)	2(18%)
65-74	3(37.5%)	7(64%)
>75	2(25%)	2(18%)

Figure 2: Male patients age- wise distribution with No. & percent

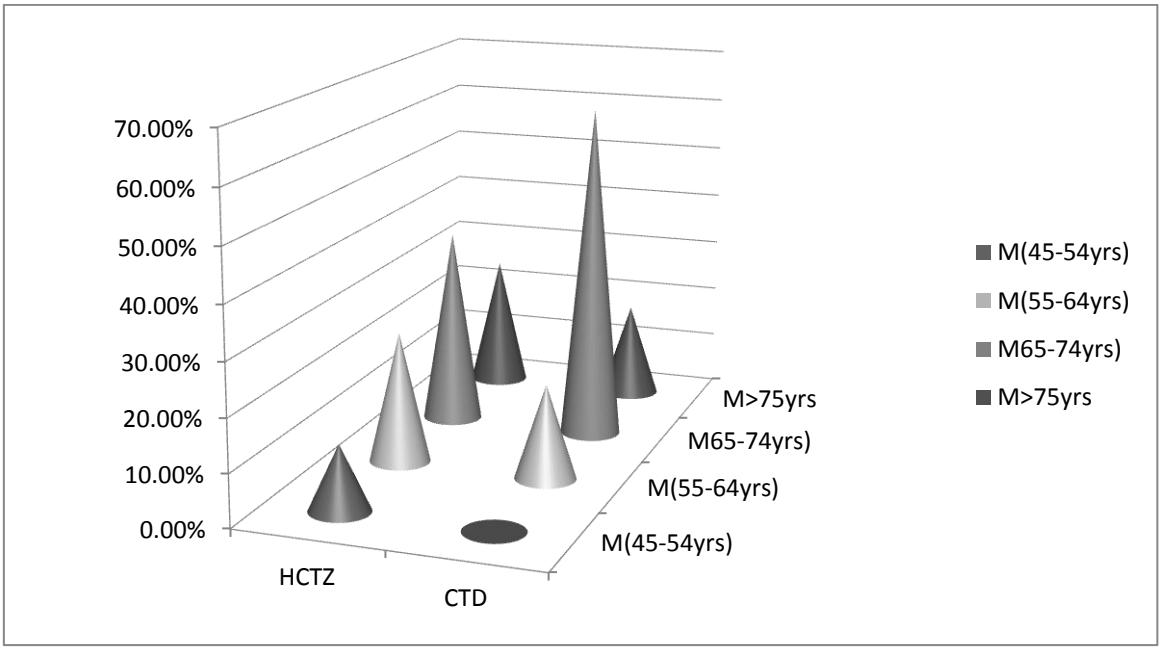

Table 4: Female patients age- wise distribution with No. & percent

Female with age in years	HCTZ(n=12)with percent	CTD(n=9) with percent
45-54	0	1(11%)
55-64	2(17%)	3(33%)
65-74	7(58%)	5(56%)
>75	3(25%)	0

Figure 3: Female patients age- wise distribution with No. & percent

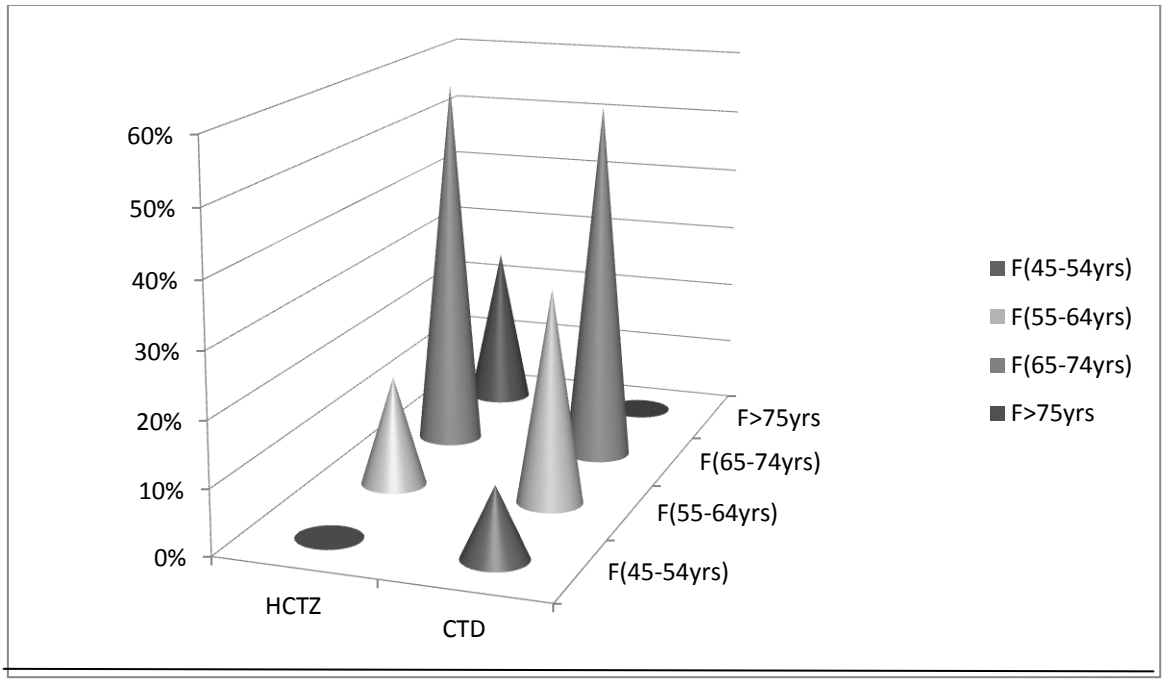

Table 5: Clinical symptoms on admission

Symptoms	Hydrochlorthiazide(n=20)	Chlorthalidone(n=20)
Anorexia & vomiting	7	10
Hiccup	5	6
Seizure	4	2
Alter sensorium	4	1
vertigo	0	1

Anorexia and vomiting were the most common complaints (table 5 & figure 4). Five patients were asymptomatic on admission and were referred for hospitalization because of incidental finding of hyponatremia. Only eight patients had serum sodium levels below 110mmol/L (table 6 & figure 5) and their age were more than sixty five along with seven were female. Serum potassium levels were normal (>3.5 mmol/L) in 37 patients (P=1).

Figure 4 Clinical symptoms on admission:

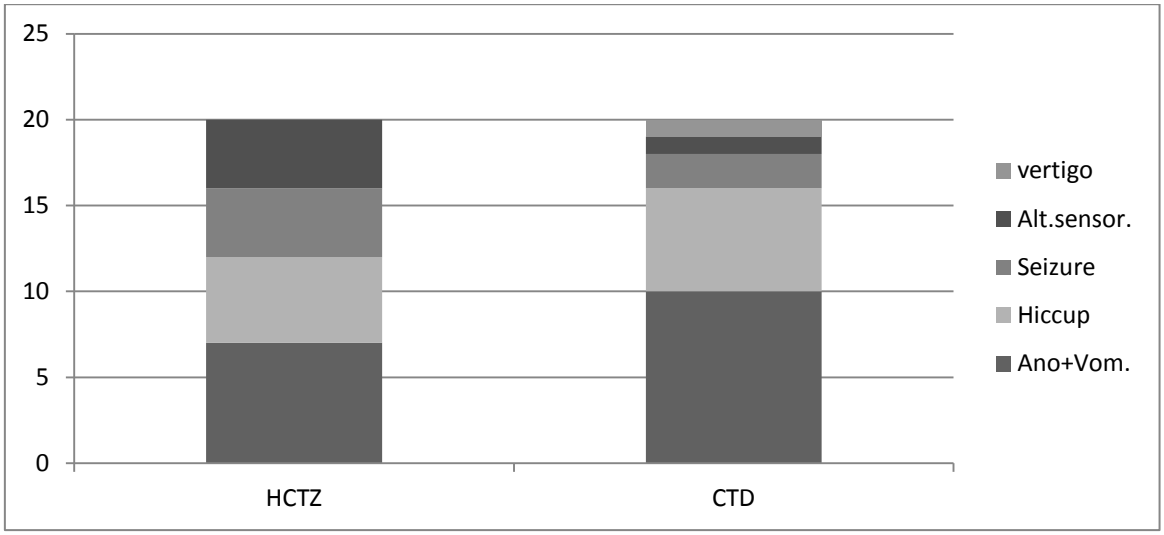

Table 6 : Serum Sodium level

Serum Na level(mg/dl)	Hydrochlorthiazide(n=20)	Chlorthalidone(n=20)
120 -134	4	12
110-119	9	7
< 110	7	1

Figure 5 Serum Sodium level

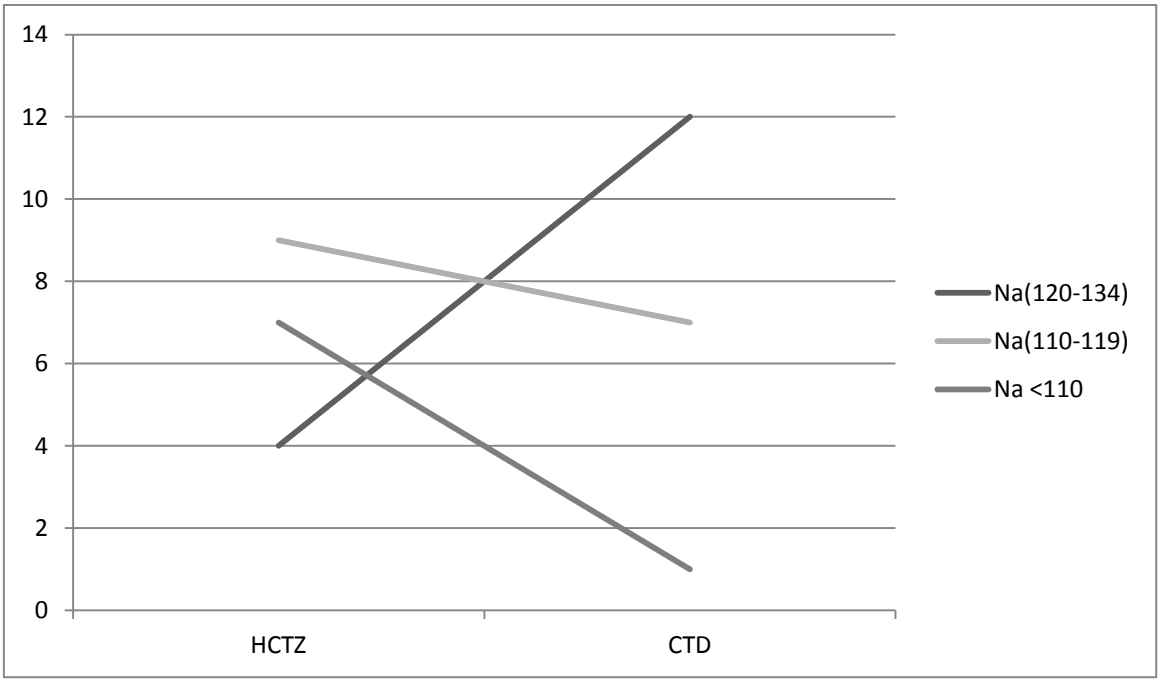

Table -7

	Hydrochlorthiazide (n=20) Mean ±SD	Chlorthalidone (n=20) Mean±SD	p- value
Serum Na (mEq/L)	113 ±8	124±6.5	< 0.0001

Significance of Severe hyponatremi in HCTZ group versus CT group ($p<0.0001$) is shown in table 7.

Discussion

Thiazide diuretics(mainly HCTZ & CTD) are often considered medications in hypertensive patients. Electrolyte disturbance ie hyponatremia is a complication with an estimated incidence of 11% in one series of 114 geriatric patients after administration of thiazide diuretics [1]. We observed that Incidence of hyponatremia both drugs are same but severity of hyponatremia more in HCTZ than CT mainly in elderly female patients. These drugs may cause hyponatremia in substantial number of patient and hyponatremia may even be more common than hypokalemia. In the SHEP study , 4.1% of the diuretic treated patients had hyponatremia and 3.9% had hypokalemia during the study [2]. Sunderam et al found among elderly patients taking diuretics that 17% developed hyponatremia compared with only 6.6% who developed diuretic induced hypokalemia [3]. Numerous case reports have indicated that hypertensive women are particularly at risk to develop hyponatremia [4-12]. As hypertensive woman are often treated with diuretics than hypertensive men [13-14], they may be more susceptible to develop hyponatremia and also more symptomatic than men at similar level of sodium. So diagnosis of hyponatremia is often in women than men [15]. In our study, we found that, across all ages, HCTZ has a ten-fold higher risk than CT to develop hyponatremia. It is said that hyponatremia may develop shortly after initiation of diuretic therapy [16]. We observed 7 patients older than 75 years, hyponatremia was developed within 15 days of treatment.

Conclusion

Elderly patients are likely to be at particularly high risk. In such cases diuretic use should be associated with close monitoring of sodium levels.

Acknowledgments

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