ORIGINAL ARTICLE

Changes in Level of Calcium in Serum and Urine in Patients on Ceftriaxone – A Prospective Study

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ABSTRACT

Introduction: Ceftriaxone is a third generation cephalosporin used to treat respiratory and urinary tract infections in children. It is known to be associated with biliary pseudolithiasis although the development of urolithiasis has been rarely reported which may be related to hypercalciuria. The aim of the study was to determine the changes in level of calcium in serum and urine in patients on ceftriaxone.

Methods: This prospective observational study was carried out on 100 patients from 1 year to 18 years of age admitted with respiratory tract illness in a tertiary care hospital from June 2019 to December 2020. Patients were divided into two groups: 50 patients as cases were treated with ceftriaxone and 50 patients as controls were treated with amoxiclav. Serum calcium, creatinine, urine calcium and creatinine, were done before and after 4 days of starting ceftriaxone and values were compared. Serum ceftriaxone levels were also measured.

Results: Both the groups were comparable in terms of age, sex distribution, pre-treatment serum calcium, urine calcium, urine calcium creatinine ratio. Paired urine samples revealed that urine calcium creatinine ratio increased significantly in cases treated with ceftriaxone (0.08±0.15 mg/mg, p=0.004 respectively). There was a positive correlation between urine calcium creatinine ratio and dose (r=0.40, p=0.005) and serum levels (r=0.30, p=0.035) of ceftriaxone. Patients treated with ceftriaxone were 5 times more likely to develop hypercalciuria as compared to amoxiclav (RR (95% CI) 5.0 (1.97 – 13.32)

Conclusion: The study demonstrates ceftriaxone increases the urinary calcium excretion and has the potential to cause significant hypercalciuria. The increase in urinary calcium excretion is dependent on the dose and level of ceftriaxone.

Keywords: Ceftriaxone; Hypercalciuria; Nephrolithiasis; Urine Calcium Creatinine Ratio.

INTRODUCTION

Ceftriaxone is a semisynthetic broad spectrum third generation cephalosporin. It is widely used due to its broad spectrum action and long life[1]. It is the drug of choice for respiratory tract and urinary tract infections[2]. Ceftriaxone is primarily eliminated via the kidneys (33-67%) and remainder via biliary system[3]. It is an anion that can bind to calcium cations in a 1:1 ratio and induce reversible precipitations, resulting in crystallization leading to nephrolithiasis[4]. The true prevalence of ceftriaxone induced nephrolithiasis is not known. The first case of ceftriaxone induced nephrolithiasis was reported by Schaad et al[5] in 1988. Two prospective studies have revealed that 1.4%-7.8% of patients developed renal calculi within 7 days of therapy[6]. Nephrolithiasis reported in children with ceftriaxone was mostly related to dose and duration of therapy[7]. Several studies in past postulated that the reaction and subsequent precipitation of ceftriaxone with calcium within renal tubules leads to disturbance of tubular reabsorption of calcium resulting in excess urinary excretion. This hypercalciuria predisposes to the development of ceftriaxone induced nephrolithiasis[1,3,5,8]. The evidences were limited and studies failed to show a strong relationship between ceftriaxone doses or its levels in serum and urine calcium excretion. Our objective was to study whether ceftriaxone causes hypercalciuria by changing the level of calcium in serum and urine in patients on ceftriaxone and its correlation with the dose and serum levels of ceftriaxone.

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MATERIAL AND METHODS

Study was conducted after seeking ethical approval from institutional ethical committee. This was a prospective observational study including 100 children of 1 year to 18 years of age hospitalized for respiratory tract infections in paediatric wards of a tertiary care hospital. Those with co-existing renal, cardiac, hepatobiliary disease, urinary tract infection, on agents causing hypercalciuria and those treated with ceftriaxone in last 10 days were excluded. Patients with family history of hypercalciuria, renal or biliary stones were also excluded. None of the patient was critically ill. Hypercalciuria was defined a urinary calcium excretion of more than 4 mg /kg per day, a random calcium/creatinine ratio of more than 0.18, or a 24-hour urinary calcium concentration of more than 200 mg/liter may be more useful. In the study urine creatinine ration was used as method for evaluation of hypercalciuria adjusted with age[9].

Patients were divided into two groups: case group (50 patients) who received intravenous ceftriaxone in a dose of 50-100 mg/kg/day in two equal divided doses and control group (50 patients) who received intravenous amoxiclav at a dose of 90 mg/kg/day in three equal divided doses. After clinical history and examination blood and urine samples were collected to measure serum levels of calcium, creatinine and ceftriaxone and urinary levels of calcium and creatinine to calculate calcium creatinine ratio. The above levels were repeated after four days of therapy in both the groups. Calcium levels in serum and urine were measured by Arsenals 3 kit method on semi-automated biochemistry analyzer. Creatinine levels in serum and urine were measured by modified Jaffe's method by spectrophotometric method on auto-analyzer. Serum ceftriaxone was measured by using High Performance Liquid Chromatography (HPLC) (UltiMate 3000, Thermo Scientific).

Statistical Methods

The comparison of changes of urinary calcium excretion average values in first and third day after admission in both groups with and with-out ceftriaxone will be performed by paired t test and chi-square test. All analysis were performed by SPSS 16, and P value less than 0.05 was considered as significant. the comparison of changes of urinary calcium excretion average values in first and third day after admission in both groups with and with-out ceftriaxone will be performed by paired t test and chi-square test. All analysis were performed by SPSS 16, and P value less than 0.05 was considered as significant. the comparison of changes of urinary calcium excretion average values in first and third day after admission in both groups with and with-out ceftriaxone will be performed by paired t test and chi-square test. All analysis were performed by SPSS 16, and P value less than 0.05 was considered as significant the comparison of changes of urinary calcium excretion average values in first and third day after admission in both groups with and with-out ceftriaxone will be performed by paired t test and chi-square test. All analysis were performed by SPSS 16, and P value less than 0.05 was considered as significant All data were expressed in number, percentage and mean. Comparison of mean of urinary calcium to creatinine ratio between day 0 and day 4 who received ceftriaxone by paired t- test. All analysis were performed by SPSS 16, and p- value less than 0.05 was considered as significant. Descriptive data was analyzed by Chi-square test. Means of different variable were compared using Wilcoxon Mann Whitney U test. Spearman correlation was used to explore the correlation between two variables

RESULTS

Table 1 shows baseline parameters of the cases and controls group. Out of total 100 patients, 64 were males and 36 females, with male: female ratio of 1.7:1. Mean age of the subjects was 6.44±4.27 years. Maximum patients were in 2-6 years of age group (43%). Mean dose of ceftriaxone was 73.80±16.40 mg/kg/day and that of amoxiclav was 90.00±0.00 mg/kg/day. After 4 days of therapy, the urine calcium creatinine ratio was not higher in cases group as compared to controls group (0.20 vs 0.12 mg/mg, p=0.136). Within cases group, the increase in urine calcium creatinine ratio was statistically significant (0.08±0.15 mg/mg, p=0.004). Table 2 and 3 shows correlation between urinary calcium excretion and ceftriaxone dose and serum levels of ceftriaxone respectively. In cases group, there was a significant positive correlation between urine calcium creatinine ratio and dose of ceftriaxone (r=0.40, p=0.005) and also between urine calcium creatinine ratio and serum level of ceftriaxone (r=0.30, p=0.035). Number of patients with hypercalciuria increased in ceftriaxone group in comparison to controls (OR 7.67 (CI 95%). The mean dose of ceftriaxone and serum level of ceftriaxone was higher in patients with hypercalciuria than in patients without hypercalciuria (79 vs 70 mg/dL, 29 vs 15 µg/dL respectively).

Table 1: Parameters between cases and controls group

Parameters	*Group*		*p value*
	Case (n = 50)	*Control (n = 50)*	
Age (Years)* **	7.75 ± 4.84	5.14 ± 3.70	0.014[1]
Age Group* **			0.017[2]
⩽2 Years	5 (10.0%)	6 (12.0%)	
2-6 Years	15 (30.0%)	28 (56.0%)	
6-12 Years	18 (36.0%)	13 (26.0%)	
>12 Years	12 (24.0%)	3 (6.0%)	
Gender			0.405[2]
Male	34 (68.0%)	30 (60.0%)	
Female	16 (32.0%)	20 (40.0%)	
Antibiotic Dose (mg/kg/day)	73.80 ± 16.40	90.00±0.00	-
S. Calcium (mg/dL) (Day 0)	9.28 ± 0.70	9.15 ± 0.50	0.367[1]
S. Calcium (mg/dL) (Day 4)	9.15 ± 0.57	9.17 ± 0.50	0.906[1]
Urinary Calcium/Creatinine Ratio (Day 0)	0.12 ± 0.09[4]	0.13 ± 0.08	0.440[1]
Urinary Calcium/Creatinine Ratio (Day 4)	0.20 ± 0.19[4]	0.12 ± 0.07	0.136[1]
Hypercalciuria (Day 0) (Present)	6 (12.0%)	5 (10.0%)	0.749[2]
Hypercalciuria (Day 4) (Present)* **	20 (40.0%)	4 (8.0%)	<0.001[2]
Change in Urinary Calcium/Creatinine Ratio* **	0.08 ± 0.16	-0.01 ± 0.04	0.033[1]

****Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Chi-Squared Test, 3: Fisher's Exact Test,4: paired t -test*

Table 2: Association between Ceftriaxone Dose and Parameters

Parameters	*Ceftriaxone Dose*	*p value*
Urinary Calcium/Creatinine Ratio (Day 4)* **	Correlation Coefficient (rho) = 0.4	0.005[1]

****Significant at p<0.05, 1: Spearman Correlation*

Table 2 shows linear increase in urinary calcium creatinine ratio on day 4 with increase in ceftriaxone dose.

Table 3: Association between Serum Ceftriaxone Levels (µg/ml) (Day 4) and urinary calcium creatinine ratio

Parameters	*Serum Ceftriaxone Levels (µg/ml) (Day 4)*	*p value*
Urinary Calcium/Creatinine Ratio (Day 4)***	Correlation Coefficient (rho) = 0.3	0.035[1]

****Significant at p<0.05, 1: Spearman Correlation*

DISCUSSION

This study was done in 100 patients to assess the effect of ceftriaxone on the levels of calcium in serum and urine. It was observed that urine calcium creatinine ratio were significantly higher in cases group treated with ceftriaxone in comparison to controls group treated with amoxiclav. There was a positive correlation between urinary calcium creatinine ratio, dose and serum level of ceftriaxone.

The mean dose of ceftriaxone used was 73.80±16.40 mg/kg/day which was within normal recommended dose and was comparable with other studies. The serum calcium was not significantly different in the two groups before and after the treatment. The serum creatinine level was significantly higher in the ceftriaxone group compared to amoxiclav group before the treatment. This was because of the predominant distribution of older children in ceftriaxone group, who have higher reference values of creatinine compared to younger children. However, no change was observed in values of serum creatinine as an effect of antibiotic administration in cases and controls group after 4 days of therapy. Our findings were similar to Kimata et al[10] whereas the other studies by Youssef et al[7] and Azarfar et al[11] found no difference in serum creatinine either before or after treatment. The levels of urine calcium creatinine ratio in cases group increased from 0.12±0.09 mg/dL to 0.20±0.19 mg/mg and in controls group the levels decreased from 0.13±0.08 mg/mg to 0.12±0.07 mg/mg. The levels before treatment were within normal range and were comparable in both the groups. But after 4 days of antibiotic therapy the levels were higher in cases group treated with ceftriaxone. The increase in urine calcium creatinine ratio within the cases group treated with ceftriaxone was significant (p=0.004) (Fig 1). This finding was similar to study by Kimata et al[10] and Esteghamati et al[2] but a study by Youssef et al[7] found no difference regarding urine calcium creatinine ratio between the groups either before or after antibiotic therapy and there was no increase in urine calcium to creatinine ratio after treatment as compared to the values before treatment initiation. A study by Azarfar[4] et al found a significant increase in calcium creatinine ratio in both ceftriaxone group and non-ceftriaxone group. In the present study, the urine calcium creatinine ratio increased by 0.08±0.15 in cases group (p=0.004) treated with ceftriaxone.

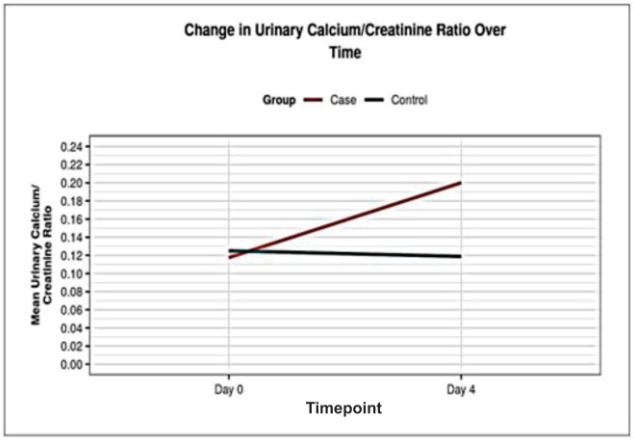

Figure 1: Line diagram depicting the urinary calcium excretion over time in both the groups

More than 95% of calcium filtered from blood is reabsorbed in renal tubules with approximately 70% of calcium being absorbed in proximal tubules, about 20-30% being absorbed in loop of Henle, 5-10% being reabsorbed in distal tubules and <5% in renal collecting tubules[12]. It is possible that ceftriaxone (anion) reacts with calcium (cation) and precipitates within renal tubules via the formation of an insoluble salt calcium ceftriaxone leading to disturbance of tubular reabsorption of calcium resulting in its excess urinary excretion[10]. Patients treated with ceftriaxone were 5 times more likely to develop hypercalciuria when compared to patients treated with amoxiclav. [RR 5 (1.97-13.32) (95% CI)]. This suggested ceftriaxone not only increases urinary excretion but increases the excretion to a significant point of hypercalciuria thereby predisposing for developing nephrolithiasis. The finding was similar to the findings of Esteghamati et al[2] and Kimata et al[10]. A significantly positive correlation was observed between urine calcium creatinine ratio after 4 days of therapy and ceftriaxone dose (rho=0.4, p=0.005). For every 1 unit increase in ceftriaxone dose, the urine calcium creatinine ratio increased by 0.04 units after 4 days of therapy (Fig 2a). Similarly, There was a significant positive correlation between urine calcium creatinine ratio and serum ceftriaxone levels after 4 days of therapy (rho=0.39, p=0.035). For every 1 unit increase in serum ceftriaxone, the urine calcium creatinine ratio increased by 0.09 units (Fig 2b). This finding suggested that ceftriaxone not only increased the urinary calcium excretion after 4 days of therapy but the increase in urinary calcium excretion was dependent on dose of ceftriaxone given and the serum

ceftriaxone levels achieved. The urinary calcium excretion was higher with higher dose of ceftriaxone and higher levels of serum ceftriaxone. Also, the dose as well as serum ceftriaxone was higher among patients with hypercalciuria when compared to patients without hypercalciuria. Mean dose (79 vs 70 mg/dL), median dose (90 vs 60 mg/dL). Mean serum level (20 vs 15 µg/ml) median serum levels (15 vs 10 µg/ml).

The study is the only study from India correlating the urinary calcium excretion with dose of ceftriaxone and serum levels of ceftriaxone. The present study has the following limitations. Results of the study maybe limited due to its small sample size, studies with larger population are suggested for further generalization of the results. Follow up of the patients was not done so we could not show whether hypercalciuria was sustained or resolved after discontinuation of ceftriaxone and thus long term complications of ceftriaxone therapy could not be assessed.

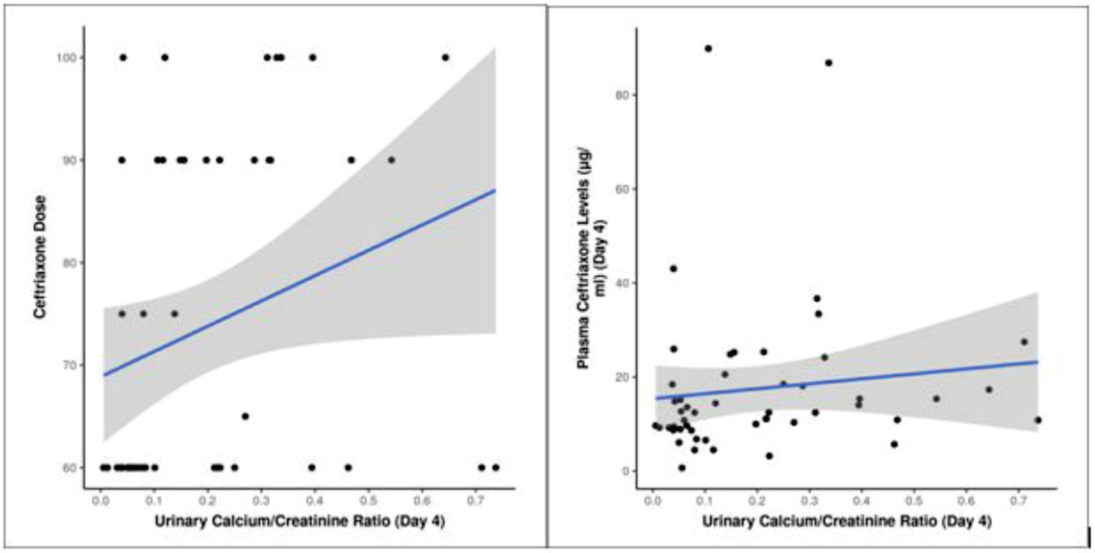

Fig 2a Fig 2B

Figure 2a and 2b: Correlation between urine calcium creatinine ratio with ceftriaxone dose and serum cefteriaxone levels

CONCLUSION

To conclude, ceftriaxone significantly increased the urinary calcium creatinine ratio after 4 days of therapy when administered in the recommended dose range. The magnitude of increase in urinary calcium excretion was dependent on the dose of ceftriaxone administered and the serum levels of ceftriaxone achieved after 4 days of therapy. Ceftriaxone even increased the urinary calcium excretion to a significant point of hypercalciuria thereby predisposing the patients for developing nephrolithiasis in the future.

Recommendation

The antibiotic ceftriaxone should be used cautiously in children as it increases the urinary calcium excretion predisposing the children for developing nephrolithiasis. It is particularly important to monitor patients treated with ceftriaxone with UCa/UCr especially on high doses and longer duration of treatment as these individuals maybe at higher risk for complications. This type of screening may help to prevent complications in future.

Conflict of interest: None

Source of funding: Multi-disciplinary research unit (MDU), DHR, ICMR

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