Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children

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Background: Background: Ceftriaxone, a third generation cephalosporin, is widely used for treating infection during childhood. The kidneys eliminate approximately 33–67% of this agent, and the remainder is eliminated via the biliary system. Ceftriaxone may bind with calcium ions and form insoluble precipitate leading to biliary pseudolithiasis. The aim of this study was to assess whether ceftriaxone associated nephrolithiasis develops by the same mechanism, and whether this condition is dose related.

Methods: The study involved 51 children with various infections. Of these, 24 were hospitalized with severe infection and received 100 mg/kg/day ceftriaxone divided into two equal intravenous doses. The other 27 patients received a single daily intramuscular injection of 50 mg/kg/day. Serum and urine parameters were evaluated before and after treatment, and abdominal ultrasonographic examinations were also carried out before and after treatment.

Results: Serum urea, creatinine, and calcium levels were normal in all patients before and after treatment. Post-treatment ultrasound identified nephrolithiasis in four (7.8%) of the 51 subjects. The stones were all of small size (2 mm). Comparison of the groups with and without nephrolithiasis revealed no significant differences with respect to age, sex distribution, duration of treatment, or dose/route of administration of ceftriaxone. The renal stones disappeared spontaneously in three of the four cases, but were still present in one patient 7 months after ceftriaxone treatment.

Conclusions: Conclusions: The study showed that children taking a 7 day course of normal or high dose ceftriaxone may develop small sized asymptomatic renal stones. The overall incidence of nephrolithiasis in this study was 7.8%.

Ceftriaxone, a third generation cephalosporin, is widely used to treat infections during childhood. Long plasma half life and single dose daily administration are the main advantages of this agent. Ceftriaxone is primarily eliminated via the kidneys (33–67%), with the remainder eliminated via the biliary system. This drug can bind with calcium ions, producing a precipitate that forms biliary sludge, also known as biliary pseudolithiasis. A number of reports since 1988 have documented biliary pseudolithiasis during ceftriaxone therapy. In addition, nine cases of ceftriaxone induced nephrolithiasis have been described to date, but no prospective investigation of this condition has been carried out. Our aim in this study was to assess for precipitation of ceftriaxone in the renal calyces of a paediatric population and to examine the possible relationship between nephrolithiasis and ceftriaxone dose.

METHODS

The study involved 51 children who were diagnosed with various types of infection between June 2002 and June 2003. Patients with renal disease, hepatobiliary disease, or any chronic illness, and patients who were already taking nephrotoxic medication were excluded. The study group included 30 girls and 21 boys, and the age range was 1 month to 14 years (mean: 3.1 years; median: 2.5 years). The types of infection were pneumonia (n = 25), pyelonephritis (n = 20), pneumonia+pyelonephritis (n = 5), lymphadenitis (n = 1), bacterial meningitis (n = 1), and mastoiditis (n = 1).

All the patients received the same ceftriaxone preparation (Rocephin). A total of 24 children were hospitalized with severe infection, and this group was treated with intravenous ceftriaxone 100 mg/kg/day divided into two equal doses. The remaining 27 patients received single daily intramuscular doses of 50 mg/kg/day ceftriaxone.

For each case, before and after treatment we recorded serum levels of calcium, urea, and creatinine, spot urine levels of calcium and creatinine, and urinalysis findings. We also assessed each child for renal symptoms and complications (colicky abdominal pain, anuria, acute renal failure). For each case of nephrolithiasis, a 24 h urine sample was collected and excretion levels of calcium, oxalate, citrate, cystine, and uric acid were measured.

In addition to the above tests, all patients underwent abdominal ultrasonography (USG) before and after ceftriaxone therapy. The same 2–5 MHz probe (Sanoline Antares, Siemens, Germany) was used in all cases. Patients who were diagnosed with nephrolithiasis underwent weekly USG exams after treatment to monitor changes in the detected stones.

For each patient, we calculated the urine calcium:creatinine ratio before and after treatment. The means for the two time points were compared to assess the effect of ceftriaxone on urinary calcium excretion.

Statistical analysis

All the statistical analyses were performed on a personal computer with SPSS (Statistical Package for Social Sciences) version 9.0 for Windows. Mann-Whitney U test was used for analyzing the differences between the mean values of age and duration of treatment of the two groups (with nephrolithiasis and without nephrolithiasis). Wilcoxon test was used to analyze differences between the mean values of urine calcium/creatinine ratios before treatment and after treatment. We have also performed $\chi^2$ analysis between the groups with respect to sex and dose. A $p$ value of less than
0.05 was considered to indicate statistical significance; all tests were two tailed and in the 95% confidence interval.

RESULTS

None of the children experienced abdominal pain or developed any renal complications during ceftriaxone therapy. All the patients’ serum urea, creatinine, and calcium levels were in the normal range before and after treatment.

None of the children showed abnormalities on abdominal USG before ceftriaxone was administered, but nephrolithiasis was detected in four (7.8%) cases after treatment. These patients were three girls and one boy, and their mean (SD) age was 1.1 (0.9) years (range: 0.6–2.5 years).

Fluid restriction was not applied to any of the patients and none of the patients had clinical or laboratory findings of dehydration during the follow up under ceftriaxone treatment.

The mean (SD) duration of treatment in the four patients with nephrolithiasis was 6.75 (0.5) days (range: 6–7 days). The mean (SD) duration of treatment in the 47 patients (20 boys and 27 girls; mean (SD) age: 3.3 (3.2) years; age range: 1 month–14 years) without nephrolithiasis was 7.2 (1) days (range: 5–10 days). Comparisons of these two groups revealed no significant differences with respect to mean age, sex distribution, duration of treatment, or dose/route of ceftriaxone treatment (table 1).

The features of the nephrolithiasis cases are summarized in table 2. One of these patients was a 2.5 year old girl who had received a 7 day course of intramuscular ceftriaxone (50 mg/kg/day) for pyelonephritis due to Escherichia coli. Her USG examination on day 7 showed biliary sludge and renal calculi disappeared within 3 weeks.

Fluid restriction was not applied to any of the patients and none of the patients had clinical or laboratory findings of dehydration during the follow up under ceftriaxone treatment.

DISCUSSION

Biliary sludge, or pseudolithiasis, is a known side effect of ceftriaxone treatment.19 This precipitated material forms when there is a high concentration of ceftriaxone in the biliary system. Normally, the liver eliminates a considerable proportion of ceftriaxone in the form of a soluble salt. However, ceftriaxone is an anion, and, when concentrations of the drug are high, these anions can bind with calcium ions to form insoluble complexes that precipitate out in the biliary system.11 It appears that stones can form in the same way in the renal collecting system. To date, nine cases of ceftriaxone related nephrolithiasis have been reported, and eight of these patients were children.11–19 In five of the nine cases, investigation with infrared spectrophotometry confirmed that the stones had developed due to ceftriaxone therapy.

In our study, post-treatment USG showed that four (7.8%) of the 51 children had developed small sized renal calculi while on ceftriaxone. Renal stones are seen on ultrasound examination as echogenic foci with posterior acoustic shadows. However, small stones may fail to demonstrate acoustic shadowing. There is no correlation between stone composition and the sonographic appearance. The clinical history is helpful to distinguish the other echogenic, non-shadowing intraluminal masses including blood clots, pyogenic debris, sloughed papillae in cases of papillary necrosis, fungus balls, and tumours from small stones.20–22 We supposed that the reaction and subsequently precipitation

| Table 1 Features of the 51 cases studied, with patients divided according to ultrasound findings after treatment. |
|---------------------------------------------------------------|--|--|--|
| **Ultrasonographic finding** | **Nephrolithiasis (n = 4)** | **No nephrolithiasis (n = 47)** | **p** |
| **Sex (M/F)** | 1/3 | 20/27 | 0.634 |
| **Age (years), mean (SD); range** | 1.1 (0.9); 0.6–2.5 | 3.3 (3.2); 0.08–14 | 0.146 |
| **Duration of treatment (days), mean (SD); range** | 6.75 (0.3); 6–7 | 7.1 (1); 5–10 | 0.151 |
| **No. of patients according to Cf dose** | | | |
| **50 mg/kg/day, im (n = 27)** | 2 | 25 | 1 |
| **100 mg/kg/day, iv (n = 24)** | 2 | 22 | |

Cf, Ceftriaxone; im, intramuscular; iv, intravenous.
of ceftriaxone with calcium ions within renal calices led to the pathogenesis. It is speculated that metabolic disturbances such as hypercalciuria, hyperuricuria, cystinuria, hyperoxaluria, and hypocitraturia may predispose to the development of nephrolithiasis. In our study, that high doses of the drug lead to biliary pseudolithiasis, but in previous reported cases, large obstructive stones were detected on the 4th day of treatment with ceftriaxone 125 mg/kg/day, and other patients on a similar dose range developed such stones at 8–10 days of treatment.

In addition to ceftriaxone dose, longer treatment time can increase a patient’s risk for renal complications and nephrolithiasis. In one previously reported case, large asymptomatic stones were detected on the 4th day of treatment with ceftriaxone 125 mg/kg/day, and other patients on a similar dose range developed such stones at 8–10 days of treatment. The mean course of treatment in our study was 7 days.

The number of cases in our nephrolithiasis group was very small, so it is impossible to make strong conclusions. However, the male:female ratio in the groups with and without nephrolithiasis was similar, which suggests no sex bias. Interestingly, the mean patient age in the nephrolithiasis group (age (SD) 1.1 (0.9) years) was significantly lower than that of the group without nephrolithiasis (3.3 (3.2) years). This suggests that young age may be a risk factor for the formation of urinary stones during ceftriaxone therapy.

CONCLUSION

Our results demonstrate that paediatric patients may develop small sized, asymptomatic renal stones during a 7 day course of normal or high dose ceftriaxone therapy. The overall incidence of nephrolithiasis in our study group (27 patients on normal dose, 24 patients on high dose) was 7.8%. It is particularly important to monitor patients on high dose long term ceftriaxone treatment with USG and renal function testing, as these individuals may be at greater risk for large stones and renal damage. This type of screening may help prevent permanent complications in future.

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Conflict of interest: none declared.

REFERENCES