

# Ceftriaxone-Associated Biliary Sludge and Pseudolithiasis in Children

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**Abstract:** Detection of incidence and the risk factors of ceftriaxone (CTX)-associated pseudolithiasis (PL) in children. One hundred fourteen patients (75 boys and 39 girls) who used CTX for the treatment of various infections were admitted to the study. Pseudolithiasis was diagnosed by ultrasonography (USG). Ultrasonography was performed at the beginning, on the 5th and 10th days, and at the end of the treatment. Weekly USG was performed to patients who had PL until the findings improved. It was investigated whether the age, sex, weight, treatment duration, dosage, and the way of administration have effects on PL development. Ceftriaxone was administered intravenously. Fifty-seven patients received once-daily and 57 patients received twice-daily dosage. Pseudolithiasis was observed in 37 (32.5%) of 114 patients. Age, sex, weight, treatment duration, and dosage had no role in PL development, whereas once- or twice-daily administration was found effective. Once-daily dosage of CTX treatment is recommended because of its lower incidence of PL development. Besides that USG should be performed regarding the risk of PL in children who are treated with CTX, further studies are necessary to determine the risk factors.

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Ceftriaxone (CTX) is a third-generation cephalosporin which can be used once or twice a day because of its wide spectrum and long plasma half-life. Because of its easy application and efficacy, it is widely used in the treatment of various infections of the pediatric age group and in surgical prophylaxis, particularly in cases who are hospitalized.<sup>1</sup> Although its primary excretion is through the kidneys, 40% of it is secreted in the bile.<sup>2</sup> It was detected that as the usage of CTX is increased particularly in children, biliary sludge and cholelithiasis, which is known as biliary pseudolithiasis (PL), will develop more frequently.<sup>1,3,4</sup>

There are many studies in the literature showing PL caused by the treatment of various infections in children and adults with CTX.<sup>1,3,5</sup> Clinical and experimental studies have shown that the dysfunction of the gallbladder, such as fasting and surgery, may have role in the development of this phenomenon.<sup>6,7</sup> Ceftriaxone-associated reversible PL is

detected by ultrasonography (USG). This prospective study aimed to detect both the incidence of PL in children treated with CTX and the secondary risk factors which might cause PL.

## MATERIALS AND METHODS

One hundred fourteen patients (75 boys and 39 girls) who were hospitalized at the pediatric clinic for the treatment of various infections were included in this study. Patients were randomly divided into 2 groups with 57 patients each. Patients in the first group were given 60 to 100 mg/kg CTX by intravenous injection as 1 dose, whereas the others in the second group had the same drug regimen in 2 divided doses. The average age of the patients was  $60.44 \pm 41.09$  months (range, 1 month to 14 years). The parents or the caregivers of the patients were informed in detail about the study, and informed consent was given by all of them.

Patients having renal and liver diseases, hemolytic anemia, malignancy, cystic fibrosis, total parenteral nutrition treatment, and drug usage (drugs which increase gallstone formation such as clofibrate and nicotinic acid) were excluded from the study. None of the patients had established conditions known to be associated with gallbladder lithiasis. Serial USG with a 3.5- and 7.7-MHz transducer (Elegra Advanced System digital Doppler USG; Siemens) was obtained from the patients by the same radiologist. Ultrasonography evaluation was performed at the beginning, on the 5th and 10th days of treatment, at the end of the treatment, and 1 month after the discharge. Patients who had PL were evaluated weekly by USG until the symptoms were completely resolved. In patients with PL confirmed by USG, the CTX therapy was stopped. High-amplitude echoes with prominent posterior acoustic shadowing (Fig. 1) were considered as the ultrasonographic findings of CTX-associated PL, whereas moderate- to high-amplitude echoes without acoustic shadowing were regarded as the biliary sludge (Fig. 2).

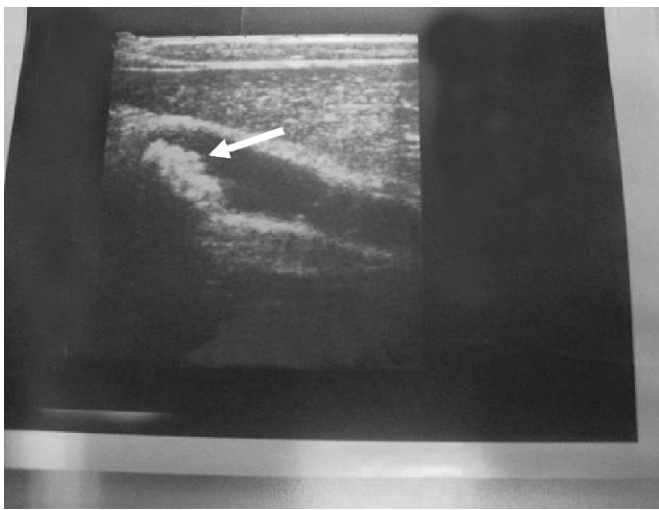
Physical examinations were performed every day. Serum calcium, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase,  $\gamma$ -glutamyltransferase, serum urea nitrogen, cholesterol, triglycerides, amylase, bilirubin, and urine analyses were performed at the initiation and termination of the treatment. Patients were investigated in 2 groups for the ones who developed PL and who did not.

Statistical analysis between the 2 groups regarding age, weight, sex, duration, and dosage of CTX treatment was made using Student *t* test, Fisher exact test,  $\chi^2$  test, and

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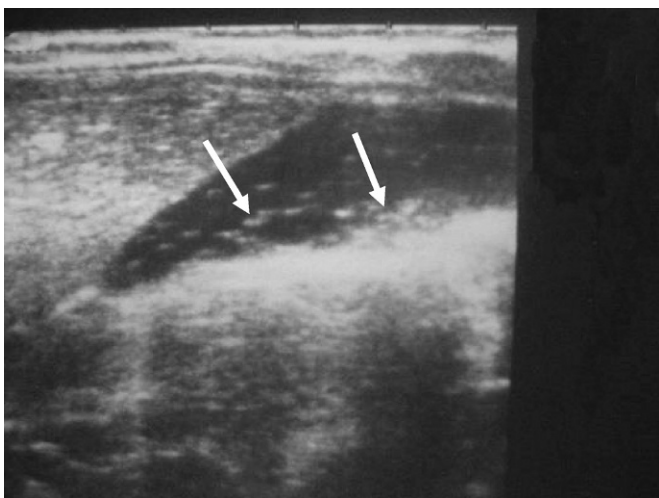
**FIGURE 1.** High-amplitude echoes with prominent posterior acoustic shadowing ultrasonographic findings of PL.

logistic regression (backward stepwise) test were used to investigate the effects of risk factors between the 2 groups.

All the variables that may contribute to the risk of PL development were analyzed (*t* test, Fisher exact test,  $\chi^2$  test). Then for detection of real risk factors, logistic regression (backward stepwise) analysis was used. In the model made for logistic regression, the drug doses were accepted as continuous variable. Female sex, age less than 2 years, weight more than 15 kg, treatment duration longer than 7 days, and drug applied in 2 doses were accepted as risk factors for the PL development, and all these factors were evaluated as grouped variable.  $P < 0.05$  was taken as statistically significant.

## RESULTS

One hundred fourteen patients were admitted to our study. In the USG evaluation of these patients, biliary sludge and gallstone were detected in 37 cases (32.5%), whereas 77



**FIGURE 2.** Moderate- to high-amplitude echoes without acoustic shadowing ultrasonographic findings of biliary sludge.

**TABLE 1.** Patient Characteristics

|                              | PL (+) Group  | PL (–) Group  | P     | ORs   |
|------------------------------|---------------|---------------|-------|-------|
| No. patients                 | 37 (32.5%)    | 77 (67.5%)    |       |       |
| Age (mo)                     | 75.30 ± 37.46 | 51.86 ± 40.78 | 0.091 |       |
| Sex (M/F)                    | 25/12         | 51/26         | 0.523 | 0.941 |
| Weight (kg)                  | 20.89 ± 8.23  | 15.71 ± 8.18  | 0.831 |       |
| Treatment duration (d)       | 8.92 ± 1.94   | 7.73 ± 2.12   | 0.268 |       |
| Dosage (mg/kg)               | 81.89 ± 14.30 | 83.78 ± 13.69 | 0.466 |       |
| Dose (single/double) (daily) | 12/25         | 44/33         | 0.007 | 0.406 |

(67.5%) cases were normal. In 7 of the patients who had abnormal USG findings, there was biliary sludge without acoustic shadowing. Clinical and treatment characteristics of the patients were given in Table 1.

No statistical difference was detected between the PL (+) and PL (–) patient groups in terms of age, sex, weight, treatment duration, and dosage ( $P > 0.05$ ). A statistically significant relation was found between the PL (+) and PL (–) patient groups in terms of single- or double-dose application ( $P < 0.05$ ). The treatment duration of the patients was  $8.12 \pm 2.13$  days (range, 5–14 days). In the PL (+) group, the duration for PL development was  $6.35 \pm 2.03$  days (range, 4–14 days), whereas the duration for the improvement of PL was  $19.27 \pm 28.57$  days (range, 4–180 days). Twenty-five (67.6%) of 37 PL (+) patients had twice-daily dose CTX, whereas the other 12 (32.4%) had once-daily dose CTX. Thirty-three PL (–) patients (42.9%) had twice-daily dose,

**TABLE 2.** Association Between PL and Age, Sex, Weight, Dose (in mg), Treatment Duration, and Single/Double Dose

|                        | n   | PL (+)        | PL (–) | P*    | Exp(B) |
|------------------------|-----|---------------|--------|-------|--------|
| Sex                    |     |               |        |       |        |
| Female                 | 75  | 13            | 26     | 0.798 |        |
| Male                   | 39  | 24            | 51     |       |        |
| Dose (mg)              | 114 | 82.02 ± 13.71 |        | 0.728 |        |
| Weight (kg)            |     |               |        |       |        |
| ≤15                    | 53  | 10            | 43     | 0.381 |        |
| ≥16                    | 61  | 27            | 34     |       |        |
| Treatment duration (d) |     |               |        |       |        |
| ≤7                     | 52  | 14            | 38     | 0.166 |        |
| ≥8                     | 62  | 23            | 39     |       |        |
| Dose (daily)           |     |               |        |       |        |
| Single                 | 57  | 13            | 44     | 0.041 | 0.398  |
| Double                 | 57  | 24            | 33     |       |        |
| Age (mo)               |     |               |        |       |        |
| 0–24                   | 36  | 3             | 33     | 0.012 | 0.171  |
| 25–72                  | 39  | 13            | 26     | 0.000 | 0.077  |
| >73                    | 39  | 21            | 18     |       |        |
| Constant               |     |               |        | 0.000 | 18.546 |

\*Backward stepwise logistic regression.

**TABLE 3.** Diseases of the Cases in the Study

|                                          | PL (+) Group | PL (–) Group | Total |
|------------------------------------------|--------------|--------------|-------|
| Meningitis                               | 23           | 32           | 55    |
| Pneumonia                                | 9            | 34           | 43    |
| Sepsis                                   | 5            | 7            | 12    |
| Pyelonephritis + urinary tract infection | —            | 2            | 2     |
| Typhoid fever                            | —            | 1            | 1     |
| Cervical abscess                         | —            | 1            | 1     |

whereas 44 (57.1%) had once-daily dose. Relationships between PL formed in pathological preparations and CTX doses (in milligrams), single- or double-dose appliances, duration of treatment, sex, age, and weight were evaluated with logistic regression analysis. As a result, sex, weight of the patient, CTX dose (in milligrams), and treatment duration were not found to be related with PL forming ( $P > 0.05$ ). However, age and CTX single/double doses usage were found to be related with PL forming significantly ( $P < 0.05$ ) (Table 3). Pseudolithiasis was 0.171 times (odds ratio [OR] = 0.171,  $P < 0.05$ ) lower in the first 24 months according to cases longer than 73 months. Besides, it was 0.077 times (OR = 0.077,  $P < 0.05$ ) lower in 25 to 72 months according to cases longer than 73 months. Also, CTX single-dose-using group had 0.398 times (OR = 0.398,  $P < 0.05$ ) lower incidence of PL.

As PL development was analyzed with age, sex, weight, treatment duration, and CTX doses with the  $t$  test, Fischer exact test, and  $\chi^2$  test, nonsignificant relations were detected, whereas with CTX single/double dose administration using logistic regression analysis with  $\chi^2$  tests, age has significant relation statistically ( $P < 0.05$ ) (Table 2).

None of the 37 PL (+) patients was symptomatic. Indications for CTX were given in Table 3.

Serum calcium, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase,  $\gamma$ -glutamyltransferase, serum urea nitrogen, cholesterol, triglycerides, amylase, bilirubin levels, and urine analyses were found within the reference range at the beginning and at the end of the CTX treatment.

## DISCUSSION

Ceftriaxone, as a third-generation cephalosporin, is eliminated not only renally but also via the biliary system. Biliary sludge in the gallbladder was detected for the first time in dogs and baboons after a prolonged duration and high dosage of CTX in a study by Teelman et al.<sup>8</sup> Later, this was also confirmed in a study in humans by Schaad et al.<sup>1</sup> The side effect of CTX is referred to as PL and is spontaneously resolved by the cessation of the treatment.<sup>9</sup>

The incidence of CTX-associated PL was reported to be 17% to 57.5% in previous studies. It was reported as 45% in a series of 37 cases in the study of Schaad et al.,<sup>1</sup> 17% in a series of 118 cases in the study of Palanduz et al.,<sup>4</sup> 25% in a series of 44 cases in the study of Papadopoulou et al.,<sup>10</sup> 26% in a series of 50 cases in the study of Ceran et al.,<sup>11</sup> and

57.5% in a series of 33 cases in the study of Ozturk et al.<sup>12</sup> We detected its incidence as 32.5% in our study.

In the analysis of biliary sludge and gallstones, precipitations have been detected as a result of interactions between bile salts, calcium, and CTX.<sup>6</sup> Gallstone formation is so rare in children, and many risk factors, such as obesity, dehydration, biliary dyskinesia, chronic hemolytic anemias, ileal resection, cystic fibrosis, Crohn disease, and drugs (such as furosemide, clofibrate, octreotide, CTX, and cyclosporin), predispose to gallstone formation.<sup>13</sup>

It has been claimed that several mechanisms play a role in the pathogenesis of CTX-associated PL. Ceftriaxone causes the unconjugate bilirubin concentration to increase by separating it from albumin. Its gallbladder concentration is 50 to 250 times more than that in the serum because of 40% excretion with bile. Ceftriaxone forms precipitations with calcium as bilirubin.<sup>14</sup> In the microscopic investigation of the developed PL, little amounts of cholesterol and bilirubin crystals but larger amounts of CTX-calcium salt were detected.<sup>15</sup>

In the PL pathogenesis, Kong and Chen<sup>7</sup> reported that being older than 2 years and a fast bile acid secretor played a role, whereas Lee et al.<sup>16</sup> asserted that surgical procedures are effective because they cause stasis in the gallbladder. In our study, all the cases were treated for various infections; none of them had surgical treatment.

Schaad et al.<sup>1</sup> claimed that CTX administration rate is effective in PL development, whereas later studies reported that this does not affect PL development.<sup>11</sup> Age, sex, weight, dose, and the treatment duration, among the other risk factors, were found to have no effect on the PL development.<sup>11,12</sup> We found similar results in our study as well. Furthermore, we investigated whether once- or twice-daily dosage of CTX has effects on the development of PL. We detected a statistically significant relation between PL development and once- or twice-daily dosage ( $P < 0.05$ ). When the cases with PL development were investigated, 25 (67.6%) of 37 cases had twice-daily dosage, whereas 12 (32.4%) had once-daily dosage. This shows a high incidence of PL development in cases with twice-daily dosage. It was detected that the incidence of CTX-associated PL was higher in cases with twice-daily dosage. We think that increased PL formation in 2-dose administration results from the drug's pharmacokinetic properties, because after ingestion of drug, its elimination starts immediately and is completed at 12 hours after the second dose is given. Repetitive doses result in increase in accumulation of drug in the body. Also, we have not found about doses of the drug and its relation with PL formation in the recent studies.

Pseudolithiasis as a complication of CTX is reversible and improves clinically and radiologically with the cessation of the drug.<sup>1–3,5</sup> It arises usually 4 to 22 days (mean, 9 days) after the initiation of the treatment and improves within 3 to 63 days (mean, 15 days) after the cessation of the treatment.<sup>1,4,5</sup> In our study, we found the development and improvement duration of PL to be  $6.35 \pm 2.03$  days (range, 4–14 days) and  $19.27 \pm 28.57$  days (range, 4–180 days), respectively. In 1 case who had PL, we detected that the PL findings improved 180 days after the cessation of CTX

treatment. None of the previous studies have reported such a long duration so far.

We found in our study that age, sex, weight, dose (60–100 mg/kg), and the treatment duration have no effects on the incidence of CTX-associated PL development, whereas once- or twice-daily dosage did have an effect. Although CTX can be administered once or twice daily, once-daily dosage is recommended because of its lower incidence of PL development. However, further studies are needed.

Overall, cases that are treated with CTX, which is widely used in children, should be monitored regarding the complication of PL, and the treatment should be ceased when complication develops. We believe that awareness of the possible PL complication during the usage of this drug will be helpful to avoid unnecessary surgical procedures.

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