

Biliary precipitation during ceftriaxone therapy: frequency and risk factors

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Ceftriaxone, a third-generation cephalosporin, is widely used for treating infection during childhood. It is mainly eliminated in the urine, but approximately 40% of a given dose is unmetabolized and secreted into bile. The aim of this study was to investigate the frequency, clinical characteristics, and outcome of biliary sludge (BS) in addition to potential contributing risk factors in children who receive ceftriaxone.

Biliary ultrasonography was performed at the time of randomization before ceftriaxone treatment was started, on the 5th and 10th days, and at the end of the treatment. If BS was detected, patients were followed-up weekly by sonographic examination until the BS or biliary lithiasis (BL) disappeared.

A total of 114 children (56 girls, 58 boys; age range: 2-180 months, mean 47.5 ± 46.3 mos) were enrolled in the study. Fourteen (12%) subjects developed BS and 10 (9%) developed BL on the 5th day of treatment. On the 10th day of treatment, 20 (18%) subjects developed BS and 15 (13%) developed BL. In total, 35 (31%) of all subjects developed biliary precipitation (BP), of whom 20 (57%) were diagnosed as BS and 15 (43%) as BL. All subjects who developed BP were found to be asymptomatic during the course of therapy. Patient age over 12 months, daily total dose of ceftriaxone of more than 2 g, and duration of treatment longer than five days were found to be associated with BP.

Ceftriaxone frequently causes transient BPs and its probability increases if the child is over 12 months of age, the dose is over 2 g/day, or the duration is over five days. Neither radiologic investigation nor the discontinuation of treatment with ceftriaxone is necessary as long as the patient is asymptomatic.

Key words: ceftriaxone therapy, biliary precipitation, biliary sludge.

Biliary sludge (BS), also called microlithiasis, microcrystalline disease, pseudolithiasis, biliary sediment, thick bile, or biliary sands, represents precipitates formed in the bile¹. Pregnancy, rapid weight loss, prolonged fasting, and total parenteral nutrition are the clinical conditions that were reported to be associated with BS²⁻⁴. Ceftriaxone is a potent semisynthetic third-generation cephalosporin. Its prolonged half-life makes it suitable for once-daily dosing. This feature has permitted the use of this antibiotic in a variety of bacterial infections in children and adults. Ceftriaxone is mainly eliminated in the urine, but approximately 40% of a given

dose is unmetabolized and secreted into bile⁵. BS in children caused by ceftriaxone therapy was first reported by Schaad et al.⁶ in 1986. The same authors later reported that precipitations in the gallbladder that mimic cholelithiasis were seen in approximately 40% of children receiving high doses of ceftriaxone and resolved spontaneously⁷. However, concerns about the possibility of BS sometimes urge the physician to request ultrasound imaging, and ceftriaxone is usually replaced by another antibiotic that is eliminated in the urine. Once BS is detected, biliary lithiasis (BL) may develop in some of the patients, and is usually followed up by a costly

follow-up ultrasound imaging series. The aim of this study was to investigate the frequency, clinical characteristics, and outcome of BS in addition to the potential contributing risk factors in children who receive ceftriaxone.

Material and Methods

This study was conducted between July 2001 and January 2003 at the Department of Pediatrics, Marmara University Hospital, İstanbul. Children (newborns were not included in the study) who had a documented bacterial infection that required antibacterial therapy with ceftriaxone were included in this study. Patients were excluded if they had a cholecystectomy, known BL, allergy to beta-lactam antibiotics, or recent therapy with ceftriaxone. Patients were randomized to receive ceftriaxone either as intravenous infusion over 30 minutes or slow bolus intravenous injection over 2 minutes, after the informed consent was obtained. Children who were treated with single-daily dose of intramuscular ceftriaxone were also included. Biliary ultrasonography was performed at the time of randomization before ceftriaxone treatment was started, on the 5th and 10th days, and at the end of the treatment. In addition, risk factors for biliary precipitations (BPs) including age and sex of subjects, route, dosage and duration of ceftriaxone therapy were documented. If BS was detected, patients were followed-up weekly by sonographic examination until the BS or BL disappeared. The ceftriaxone therapy was not switched to another antibiotic as long as the patient remained asymptomatic. The radiologist who performed the ultrasonography did not know by which route the patient received ceftriaxone. The study was approved by the Ethics Committee of Marmara University Medical School. Chi-square or Fisher's exact test was used to assess the relationship between risk factors and BP. Relationships are expressed as odds ratio (ORs). The uncertainty in values for ORs was described by 95% confidence intervals. Analyses were undertaken in STATA V7.0 (Stata Corporation Texas, USA). A P value >0.05 was considered statistically significant.

Results

A total of 114 children (56 girls, 58 boys; age range: 2-180 months, mean 47.5 ± 46.3 mos) were enrolled in the study. The indications for ceftriaxone therapy were meningitis, bacteremia,

urinary tract infection, and other bacterial infections (including soft tissue infections and pneumonia) in 42 (37%), 33 (29%), 21 (18%), and 18 (16%) patients, respectively. None of the subjects had predisposition for BS formation including total parenteral nutrition, dehydration, rapid weight loss, or prolonged fasting. Ceftriaxone was given by intravenous infusion over 30 minutes, slow bolus intravenous injection over 2 minutes, or single-daily dose of intramuscular route in 47 (41%), 47 (41%), and 20 (18%) patients, respectively. The mean (+SD) duration of ceftriaxone therapy was 7.3 (2.6) days (range, 3 to 14 days).

No gallbladder precipitation was detected by sonographic examination in any patient at enrollment. During the ultrasonographic follow-up, 14 (12%) subjects developed BS and 10 (9%) developed BL (Fig. 1) on the 5th day of treatment. On the 10th day of treatment, 20 (18%) subjects developed BS and 15 (13%) developed BL. In total, 35 (31%) of all subjects developed BPs, of whom 20 (57%) were diagnosed as BS and 15 (43%) as BL. All of the patients who developed BP were found to be asymptomatic during the course of therapy.

On the follow-up ultrasonography, BS and BL disappeared in a mean of 21 ± 10 days and 25 ± 10 days, respectively.

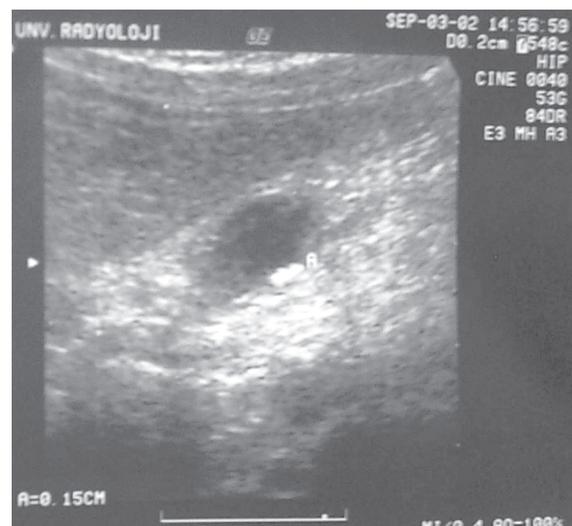


Fig. 1. Sonogram of the gallbladder of one of the patients who developed biliary lithiasis; A: indicates the biliary calculi.

The univariate analysis of patient characteristics and potential contributing factors revealed that patient age over 12 months, daily total dose of ceftriaxone of more than 2 g, and duration of treatment longer than five days were associated with BP (BS or BL) (Table I).

However, ceftriaxone-associated pseudolithiasis may cause upper abdominal pain¹², biliary obstruction^{13,14}, or pancreatitis¹⁴. Several risk factors have been investigated for formation of BPs during ceftriaxone therapy; however, findings were contradictory. We did not detect

Table I. Characteristics of Patients With and Without Biliary Precipitation (BP)

Characteristic	No (%) with BP	No (%) without BP	OR	P-value	95% CI
Age >12 months	31	41	7.1	0.0002	2.20-30.14
Male gender	19	39	1.21	0.6	0.5-2.92
Intravenous infusion over 30 min	19	28	2.16	0.06	0.9-5.2
Slow bolus intravenous injection over 2 min	13	34	0.78	0.06	0.31-1.90
Single daily dose of intramuscular injection	3	17	0.34	0.07	0.06-1.32
High dose (100 mg/kg/day)	30	59	2.03	0.14	0.64-7.58
High daily dose (>2 g)	22	11	10.4	0.0001	3.73-29.72
Longer duration of treatment (>5 days)	27	39	3.4	0.005	1.31-9.83

OR: Odds ratio. 95% CI: 95% Confidence interval.

Discussion

In our study, 31% of subjects treated with ceftriaxone developed BPs: 60% of these precipitates appeared as BS and 40% appeared as BL on sonographic examination. We found that 69% of these precipitates appeared on the 5th day of ceftriaxone therapy and the remaining were diagnosed 10 days after the first ceftriaxone dose. In addition, we have shown that BPs resolved 10-45 days (mean 7 days) after cessation of the treatment. Ceftriaxone is concentrated in the bile after excretion and its concentration can be 20-150 times higher in the bile than in the serum^{8,9}. Studies in dogs have shown that high doses of ceftriaxone given for prolonged periods of time caused gallbladder precipitates, and these precipitates contained 30-50% taurocholic acid, 10% lecithin and 30-40% calcium salts of ceftriaxone¹⁰. The frequency of biliary pseudolithiasis among patients who were treated with high doses of ceftriaxone was reported as about 40% in children⁷ and 25% in adult patients¹¹. BPs generally develop 4-22 days after ceftriaxone treatment is started and completely resolve 2-63 days after the end of treatment⁷. However, Blais and Duperval¹² reported a case who developed BS after two days of ceftriaxone therapy.

In our study, none of the subjects who developed BPs had clinical complaints. Generally, previous studies have shown that the biliary pseudolithiasis is asymptomatic^{7,11}.

sex to be a risk factor, but age above 12 months was significantly associated with BP, similar to Schaad's findings⁷. Ceftriaxone dose over 2 g/day and for a duration of longer than five days were found to be associated with BP in our study. It was previously shown that frequency of BP increases with ceftriaxone dose over 2 g/day^{13,15}, or over 100 mg/kg/day¹². In contrast, in another pediatric study, dose (50 mg/kg/day vs. >50 mg/kg/day) and duration (<5 days vs. >5 days) of ceftriaxone therapy were not found to be risk factors for BP¹⁶.

The route of the ceftriaxone administration was also thought to be a main determinant of BP. Administration of ceftriaxone either by intravenous bolus injection over 2 minutes, slow intravenous infusion over 30 minutes, or single daily dose by intramuscular route did not have an impact on the frequency of BP. Schaad et al.⁷ demonstrated the incidence of BP was lower in patients who received ceftriaxone by intravenous infusion compared to intravenous bolus injection, but in that study they investigated 37 patients, 16 of whom developed BPs. Since the study was done in a small patient population and this clinical data has not been supported by any experimental data, we cannot conclude that route of ceftriaxone administration determines the occurrence of BS.

In conclusion, ceftriaxone frequently causes transient BPs and its probability increases if the child is over 12 months of age, the dose is over

2 g/day, or the duration is over five days. Neither radiologic investigation nor the discontinuation of treatment with ceftriaxone is necessary as long as the patient is asymptomatic.

REFERENCES

1. Lee SP, Maher K, Nicholls JF. Origin and fate of biliary sludge. *Gastroenterology* 1988; 94: 170-176.
2. Maringhini A, Marceno MP, Lanzarone F. Sludge and stones after pregnancy. *J Hepatol* 1987; 5: 218-223.
3. Shiffman ML, Sugerman HJ, Kellum JM. Gallstone formation after rapid weight loss: a prospective study in patients undergoing gastric bypass surgery for treatment of morbid obesity. *Am J Gastroenterol* 1991; 86: 1000-1005.
4. Messing B, Bories C, Kuntslinger F. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? *Gastroenterology* 1983; 84: 1012-1019.
5. Avidsson A, Alvan G, Angelin B, Borga O, Nord CE. Ceftriaxone: renal and biliary excretion and effect on colon microflora. *J Antimicrob Chemother* 1982; 14: 213-217.
6. Schaad UB, Tschaeppler H, Lentze MJ. Transient formation of precipitations in the gallbladder associated with ceftriaxone therapy. *Pediatr Infect Dis* 1986; 5: 708-710.
7. Schaad UB, Wedgwood-Krucko J, Tschaeppler H. Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet* 1988; 2: 1411-1413.
8. Park HZ, Lee SP, Schy AL. Ceftriaxone-associated gallbladder sludge. *Gastroenterology* 1991; 100: 1665-1670.
9. Richards DM. Ceftriaxone. A review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1984; 27: 469-527.
10. Cometta A, Gallot-Lavallee-Villars S, Iten A, et al. Incidence of gallbladder lithiasis after ceftriaxone treatment. *J Antimicrob Chemother* 1990; 25: 689-695.
11. Pigrau C, Pahissa A, Gropper S, Sureda D. Ceftriaxone-associated biliary pseudolithiasis in adults. *Lancet* 1989; 2: 165.
12. Blais C, Duperval R. Biliary pseudolithiasis in a child associated with 2 days of ceftriaxone therapy. *Pediatr Radiol* 1994; 24: 218-219.
13. Jacobs RF. Ceftriaxone-associated cholecystitis. *Pediatr Infect Dis J* 1988; 7: 434-436.
14. Zinberg J, Chernaik R, Coman E, Rosenblatt R, Brandt LJ. Reversible symptomatic biliary obstruction associated with ceftriaxone pseudolithiasis. *Am J Gastroenterol* 1991; 86: 1251-1254.
15. Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med* 1990; 322: 141-147.
16. Kong MS, Chen CY. Risk factors leading to ceftriaxone-associated biliary pseudolithiasis in children. *Chang Keng I Hsueh* 1996; 19: 50-54.