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Ceftriaxone-associated biliary pseudolithiasis in paediatric surgical patients

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Abstract

It is well known that ceftriaxone leads to pseudolithiasis in some patients. Clinical and experimental studies also suggest that situations causing gallbladder dysfunction, such as fasting, may have a role for the development of pseudolithiasis. In this study, we prospectively evaluated the incidence and clinical importance of pseudolithiasis in paediatric surgical patients receiving ceftriaxone treatment, who often had to fast in the post-operative period. Fifty children who were given ceftriaxone were evaluated by serial abdominal sonograms. Of those, 13 (26%) developed biliary pathology. Comparison of the patients with or without pseudolithiasis revealed no significant difference with respect to age, sex, duration of the treatment and starvation variables. After cessation of the treatment, pseudolithiasis resolved spontaneously within a short period. The incidence of pseudolithiasis is not affected by fasting.

Keywords: Pseudolithiasis; Ceftriaxone; Cholelithiasis; Gallbladder

1. Introduction

Ceftriaxone (CTX); a potent, semisynthetic, third-generation cephalosporin has excellent antimicrobial activity against Gram-positive and Gram-negative bacteria [1]. It is widely used in serious bacterial infections including intra-abdominal infections and surgical prophylaxis.

It was reported that CTX could induce reversible gallbladder sludge and/or lithiasis named pseudolithiasis (PL) [2,3]. In the literature, there are a number of studies addressing the occurrence and incidence of PL in children and adults who have received CTX for infectious diseases [2–6]. Clinical and experimental studies suggest that situations causing gallbladder dysfunction, such as fasting, may have a role for the development of this phenomenon [7,8]. In this study, we evaluated prospectively the incidence and clinical importance of PL in paediatric surgical patients who often have to fast in the post-operative period.

2. Materials and methods

Fifty paediatric patients, who were to undergo abdominal operations for a variety of surgical diseases, were included into the study after informed consent was obtained from the parents. All patients were given same drug regimen (100 mg/kg/day CTX in two divided doses by bolus intravenous injections) and were maintained in a state of good hydration. Patients having renal or liver failure, ileal dysfunction, haemolytic anaemia, malignancy, cystic fibrosis, Wilson disease and those receiving total parenteral nutrition were excluded from the study. None of the patients were exposed to drugs such as clofibrate, nicotinic acid or substances and conditions known to be associated with gallbladder lithiasis.

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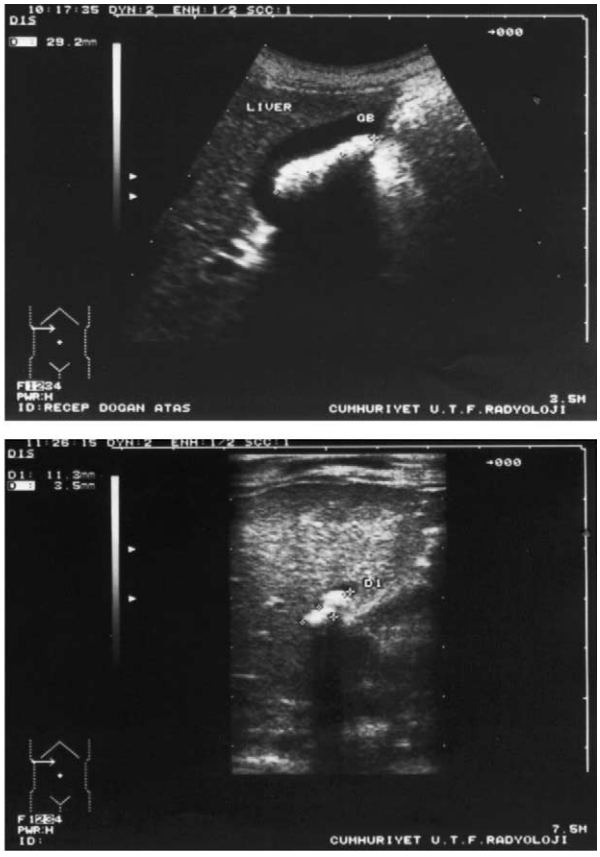
Patients were evaluated by serial abdominal sonograms performed by the same radiologist with a 3.5 MHz transducer (Hitachi 515 EUB). Patients were examined prior to and at the end of the CTX treatment, or more often if the patients showed symptoms related to PL. When abdominal sonography demonstrated gallbladder lithiasis, control sonograms were obtained every week until the resolution of the PL was documented sonographically.

The presence of hyperechogenic material in the gallbladder with post-acoustic shadowing in addition to changes in echo pattern and fluid–fluid level indicative of bile sludge (Fig. 1a and b), was considered to be biliary PL.

Physical examinations were performed every day. Serum calcium, alanine and aspartate aminotransferase, γ-glutamyl-transferase, alkaline phosphatase, amylase, bilirubin levels and urine analysis were routinely performed for all patients at the initiation of treatment and repeated synchronously with the ultra sound examinations of patients who developed PL.

Patients were evaluated in two groups; group A consisted of patients who developed PL during CTX treatment and group B those who did not develop PL during CTX treatment. Statistical analysis between the two groups regarding age, weight, sex, duration of CTX treatment and duration of starvation were made by Student's *t*-test. Statistical analysis between the two groups for primary surgical diseases and sex were made using the Chi-square test. $P < 0.05$ value was taken as statistically significant.



(a)

(b)

Fig. 1. (a) and (b) Ultrasonographic appearance of two cases showing pseudolithiasis. There is hyperechogenic material in the gallbladder with post-acoustic shadowing.

3. Results

Fifty children were evaluated in this study. Clinical and treatment data of all patients are presented in Table 1. Twelve (24%) of the patients developed mobile, gravity-dependent echogenic material accompanied by clear acoustic shadowing and one (2%) patient had changes in the echo pattern and fluid–fluid level indicative of biliary sludge (Fig. 1a and b). The rest of the patients ($n = 37$, 74%) had normal findings on abdominal sonography at the end of the treatment. In all patients who developed PL, ultrasonographic examinations revealed completely normal findings at the seventh day after the cessation of CTX treatment.

There was no statistically significant difference between the two groups regarding sex, age, body weight, duration of CTX treatment, and duration of starvation ($P < 0.05$). Duration of CTX treatment was 3–10 days (mean 8 days).

The indications for hospitalization are listed in Table 2. Most common indications were perforated appendicitis and intra-abdominal abscess. There was no significant relation between PL incidence and primary surgical diseases of the patients ($P < 0.05$).

The mean starvation period was 3.3 ± 1.1 days for group A and 2.5 ± 1.3 days for group B. Good hydration of the patients was maintained during the fasting period. There was no significant relation between the fasting period and incidence of PL ($P > 0.05$).

Serum calcium, alanin and aspartate aminotransferase, γ-glutamyl transferase, alkaline phosphatase, amylase, bilirubin levels and urine analysis results were within the normal range in all patients at the beginning and at the end of the CTX treatment.

Table 1
Characteristics of the patients

	Group A, PL (+)	Group B, PL (−)
Number of patients	13 (26%)	37 (74%)
Age (year)	6.8 ± 4.5	8.9 ± 5
Sex (F/M)	9/4	28/9
Weight (kg)	21.7 ± 9.8	28.5 ± 14.3
Fasting time (day)	3.3 ± 1.1	2.5 ± 1.3
Treatment duration (day)	8.8 ± 1.3	7.9 ± 2.0

Table 2
Surgical diseases of the children

Surgical diseases of the patients	PL (+)	PL (−)	Total
Perforated appendicitis	6	16	22
Acute appendicitis	1	8	9
Intra-abdominal organ injury	2	8	10
Colonic surgery	3	3	6
Other	1	2	3

4. Discussion

Post-mortem studies performed in dogs and baboons have shown precipitations of the calcium salt of CTX in the gallbladder after administration of large doses for a prolonged duration [9]. Schaad et al. [10] described a case that sonographically demonstrated precipitation in the gallbladder during CTX therapy in 1986. Following this, they evaluated 37 children treated with CTX for serious infections and reported that 17 of them (45%) developed biliary PL. They observed that the ultrasonographic abnormalities resolved after the cessation of the CTX treatment [2]. Palanduz et al. [6] evaluated 118 children with sonography and found that 17% of them had PL. Papadopoulou et al. [5] reported the PL incidence as 25%. In the present study, 26% (13/50) of the patients treated with CTX developed PL and this incidence is consistent with previous studies, except that of Schaad.

It was reported that short bolus infusions of CTX over 3–5 min were associated with a PL incidence of 55%. However, the incidence decreased to 29% when the drug was administered by 30-min infusions [2]. In the present study, bolus infusion of CTX was associated with a much lower rate than that reported by Schaad et al. and was consistent with the incidences given for other studies [2]. The present study suggests that the route of administration of the drug does not affect the risk of PL development.

In a study, analysis of gallbladder sediments of two adult patients who underwent cholecystectomy because of symptomatic CTX-associated biliary PL revealed only small amounts of cholesterol and bilirubinate, and a trace of CTX, but a high content of other calcium salts [11]. In the literature, there are some reports addressing the pathogenesis of CTX-related PL. The effect of CTX on bile flow and biliary electrolyte secretion was evaluated and it was shown that CTX had no effects on bile flow and biliary electrolyte secretion in guinea pigs, even when given at high doses [12].

Shiffman et al. [7] performed an in vitro study and evaluated possible interactions between calcium, bile salts, and CTX. They speculated that the development of biliary sludge induced by CTX results from a solubility problem, which occurs in the patients receiving high-dose treatment ($\geq$2 g). They also predicted that CTX-induced biliary sludge would not develop at low doses in patients with normal gallbladder motility [7]. However, severely ill patients who are nil by mouth and/or those receiving total parenteral nutrition have little stimulus for gallbladder contraction and thus have a greater risk to develop PL. Shiffman et al. [7] suggested that clinical studies are required to verify these predictions and to identify specific patient populations at greatest risk for developing this process. Kong et al. [8] evaluated paediatric patients who had received CTX therapy for probable or definite bacterial enteritis and reported that fasting and an age older than 24 months were probably the significant risk factors associated with the formation of PL. Lee et al. [13] reported that patients recovering from major surgery presumably have an increased risk, because of gallbladder stasis.

Fasting and surgery have been accused of increasing the risk of PL. However, all studies aimed to determine the incidence of PL have been performed on patients treated for serious bacterial infections. In this study, paediatric surgical patients who often had to be fasted were evaluated for the first time. Mean starvation times were 3.3 ± 1.1 days for group A and 2.5 ± 1.3 days for group B (Table 1). Although all of the patients underwent an abdominal operation and had to fast during the CTX treatment in this study, the incidence of PL was comparable with the previous studies.

In general, PL occurs after 4–22 days (mean 9 days) of CTX therapy, and completely resolves after 3–63 days (mean 15 days) from the cessation of the treatment [2,3,5,6]. The present study was established only to investigate the incidence of development of PL regardless of the time it forms in surgically treated children. Therefore, ultrasound examinations were done at the end of the CTX treatment and repeated at the seventh day after cessation of the treatment in patients with PL. At the seventh day, control ultrasound examination after discontinuation of CTX showed all gallbladder abnormalities to have disappeared.

Cometta et al. compared patients who received CTX and those who received amoxicillin/clavulanate 6–12 months after the treatment and concluded that CTX did not appear to lead to gallstone formation more frequently than antibiotics that are not eliminated through the bile [12].

This study suggests that development of PL is unpredictable and independent of the age, body weight, sex, duration of CTX treatment in paediatric surgical patients. Primary surgical diseases of the children, with and without PL, were also similar in the present study.

In conclusion, CTX-associated PL of the gallbladder is not uncommon and has little clinical importance because of its asymptomatic nature and tendency for spontaneous resolution. Fasting seems unrelated with PL. Knowledge of this pathology is important in order to prevent unnecessary cholecystectomies.

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