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Apparent Biliary Pseudolithiasis during Ceftriaxone Therapy

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Biliary pseudolithiasis has been reported in patients who received ceftriaxone therapy. To examine this phenomenon further, serial gallbladder sonograms were evaluated in 44 adult patients who received intravenous ceftriaxone at 2 g or a placebo daily for 14 days in a double-blind controlled study. Ultrasound examinations of gallbladders were performed on days 1 and 14 of therapy and 2 weeks posttherapy if abnormalities were observed on day 14. Eight patients were unevaluable because of abnormal base-line gallbladder sonograms. Thirty-six patients (ceftriaxone, $n = 28$; placebo, $n = 8$) demonstrated normal base-line gallbladder sonograms and were evaluated for the development of change. A total of 6 of 28 (21.4%) ceftriaxone-treated patients and 1 of 8 (12.5%) patients who received the placebo demonstrated abnormal gallbladder sonograms on day 14 ($P = 0.491$). Four of the six ceftriaxone-treated patients demonstrating abnormal sonograms were clinically asymptomatic, while two patients reported vomiting. The abnormal sonograms of gallbladders of patients treated with ceftriaxone returned to normal between 9 and 26 days posttherapy. These data suggest an association between ceftriaxone treatment and the development of gallbladder abnormalities on ultrasound examination which resolve spontaneously on discontinuation of ceftriaxone therapy.

The term pseudolithiasis has been used previously (K. Heim-Duthoy, E. Caperton, G. Matzke, and P. Peterson, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 556, 1988) to report the preliminary findings of the study reported here. Pseudolithiasis was used to describe sonographic abnormalities in the gallbladders of patients treated with ceftriaxone in an attempt to differentiate the reversible abnormalities which have been observed in ceftriaxone-treated patients from those of true operative stones.

Biliary pseudolithiasis has been reported in patients, including children, who have received high-dose intravenous bolus ceftriaxone therapy (3–5). Although these patients may or may not demonstrate symptoms, several symptomatic patients have undergone surgery. It is unclear whether biliary pseudolithiasis associated with ceftriaxone therapy is of clinical importance, and the need for surgical intervention has not been well-defined for individuals in any age group.

This study was designed to (i) determine the frequency of abnormal findings, including stone(s) as well as sludge, on gallbladder sonograms (apparent biliary pseudolithiasis) during ceftriaxone or placebo treatment in adult patients with arthritis and positive titers for Lyme disease; (ii) ascertain the nature and frequency with which symptoms associated with altered biliary function are present in these patients; and (iii) evaluate whether the gallbladder abnormalities which develop during ceftriaxone therapy resolve spontaneously upon discontinuation of ceftriaxone.

MATERIALS AND METHODS

Patients 18 years of age or older with two antibody titers to *Borrelia burgdorferi* of 1:64 or greater and stable, chronic arthritis were evaluated in an addendum to a double-blind, placebo-controlled outpatient study of ceftriaxone efficacy (unpublished data). Males and nonpregnant, nonlactating females were eligible to participate in the study if they had no history of hypersensitivity to cephalosporins. None of the patients had evidence of hepatic or obstructive biliary disease or significant renal impairment. No patients had received antibiotic therapy within 1 week prior to study initiation, and none of the patients received other antimicrobial agents concurrently. Written, informed consent was obtained from all patients who participated in the study.

This addendum study in which we evaluated serial gallbladder sonograms was initiated midway through an ongoing, larger study assessing ceftriaxone efficacy in patients with positive titers for the Lyme disease agent, *B. burgdorferi*. At the time of entry into the study, each patient was randomly assigned to receive ceftriaxone (2 g; Rocephin, lot no. C126694-01; Hoffmann-La Roche Inc., Nutley, N.J.) or placebo (0.9% sodium chloride) in a daily 30-min intravenous infusion for a total treatment duration of 14 days. The randomization ratio of patients who received ceftriaxone to those who received placebo in the planned efficacy evaluation was originally 2:1. Patients who received placebo had the option of subsequently crossing over to receive ceftriaxone.

Gallbladder ultrasound examinations were performed on days 1 and 14 of therapy. Patients demonstrating an abnormal gallbladder sonogram on day 1 were excluded from further evaluation. Follow-up gallbladder ultrasound examinations were completed 2 to 3 weeks posttherapy if abnormalities were detected at day 14. Patients with persistent gallbladder abnormalities were followed until the abnormality was resolved.

Gallbladder ultrasound examinations were performed with a sector, real-time ultrasound scanner (Ultramark 4 or 8; Advanced Technologies Laboratory Machine, Bothell, Wash.). A 3.0- or 3.5-MHz transducer was used in most

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TABLE 1. Patient demographic characteristics[a]

Treatment group	No. of evaluable patients	Sex (M/F[b])	Age (yr)	Creatinine clearance (ml/min)	Wt (kg)	Treatment duration (days)
Ceftriaxone	28	8/20	39.8 ± 14.8	105.9 ± 23.6	67.9 ± 12.4	13.8 ± 0.8
Placebo	8	3/5	45.4 ± 16.0	87.0 ± 40.5	79.3 ± 15.0[c]	14.0 ± 0.0

[a] Values are means ± standard deviations.
[b] M, Male; F, female.
[c] $P < 0.05$.

patients; a 5-MHz transducer was used in thinner patients. Patients were routinely studied in both the supine and left posterior oblique positions and, if necessary, in an upright, sitting position. Longitudinal and transverse images of the right upper quadrant were obtained, with emphasis on the gallbladder and biliary tree. Gallstones were diagnosed by demonstrating intraluminal echoes which had acoustical shadowing and were usually mobile with patient repositioning. Echogenic bile without acoustical shadowing was considered sludge. All results were interpreted by the same investigator, who was blinded to treatment randomization and treatment order.

Clinical evaluations, i.e., medical history, physical examination, and laboratory evaluation, were performed pretherapy, during therapy (day 7), posttherapy, and at the time of follow-up if symptomatology or sonographic changes were detected.

Significant differences in demographic characteristics between groups were assessed by an independent t test. Sex distribution differences between groups were assessed by a chi-square analysis. The incidence of gallbladder abnormality developments in patients who received placebo or ceftriaxone were evaluated by a chi-square analysis. Statistical significance was assessed at a level of $P < 0.05$.

RESULTS

A total of 44 patients were randomized to received either ceftriaxone or placebo and underwent initial gallbladder ultrasonography. Eight patients (two who received placebo and six who received ceftriaxone) were unevaluable because of abnormal gallbladder sonograms on day 1. The demographic characteristics of the 36 evaluable patients in the corresponding treatment groups are presented in Table 1.

Abnormal gallbladder sonograms were demonstrated on day 14 in 1 of 8 (12.5%) and 6 of 28 (21.4%) evaluable patients treated with placebo and ceftriaxone, respectively. The difference between the two groups was not statistically significant ($P = 0.491$). The characteristics of the seven patients who developed apparent biliary pseudolithiasis are

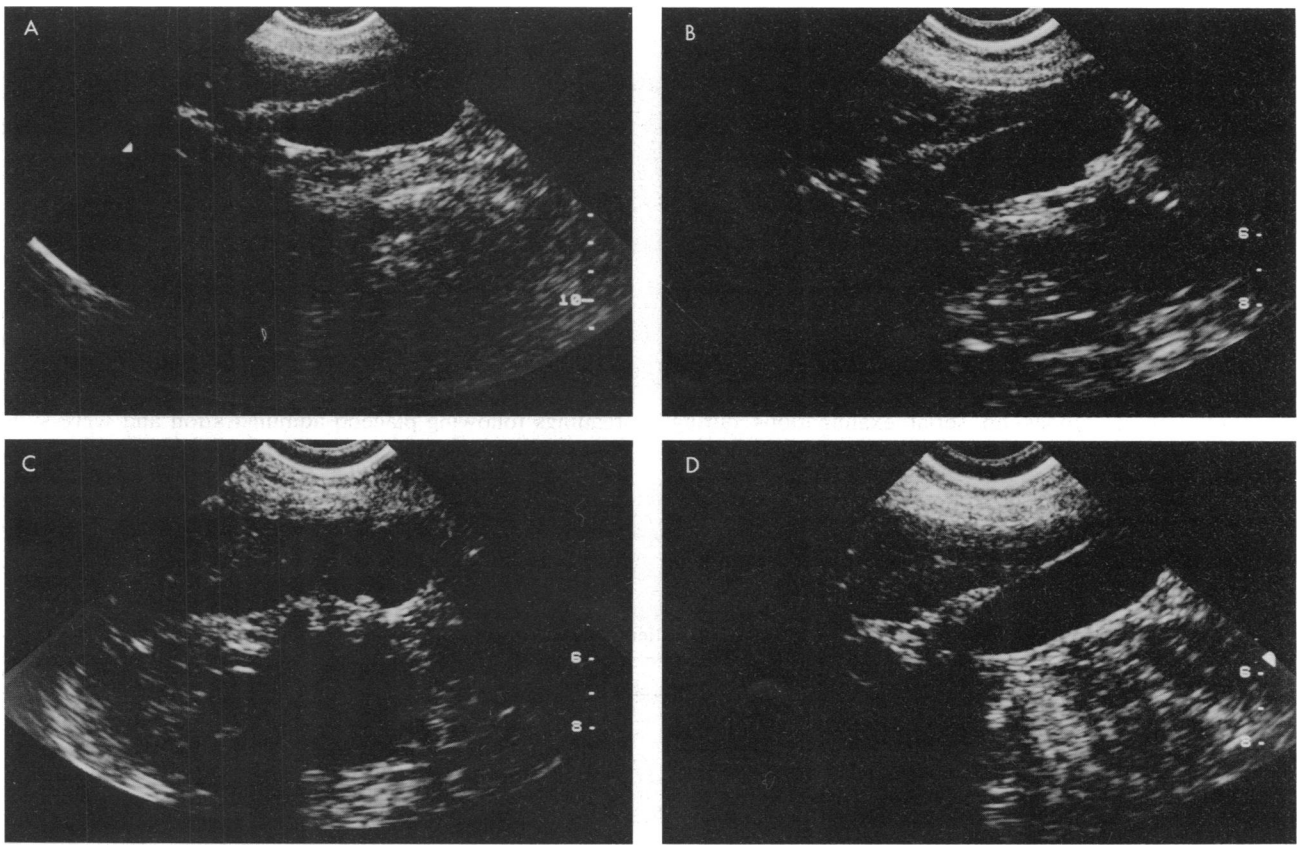

FIG. 1. Sequential gallbladder sonograms for patient 38 on days 1 (A) and 14 (B and C) of therapy and at the time of follow-up (D).

TABLE 2. Characteristics of patients who developed apparent biliary pseudolithiasis

Patient no.	Treatment group	Age (yr)	Sex[a]	Wt (kg)	Diagnosis	Treatment duration (days)	Dose (mg/kg per day)	Sonographic interpretation	Clinically symptomatic	Time of abnormality resolution (days[b])
30	Ceftriaxone	64	F	64.0	Atypical arthritis	14	31.3	Stones	No	24
38	Ceftriaxone	56	F	71.8	Atypical arthritis	14	27.9	Stones	Yes	14
41	Ceftriaxone	39	F	61.4	Atypical arthritis	14	32.6	Stones	Yes	26
45	Ceftriaxone	37	F	52.7	Vasculitis	14	38.0	Sludge	No	9
49	Ceftriaxone	32	F	56.8	Rheumatoid arthritis	14	35.2	Stones	No	14
54	Ceftriaxone	54	F	63.6	Rheumatoid arthritis	12	31.4	Single stone	No	21
46	Placebo	42	M	90.9	Psoriatic arthritis	14	NA[c]	Sludge	No	44

[a] F, Female; M, male.
[b] Days after the end of therapy.
[c] NA, Not applicable.

presented in Table 2. Two patients who received ceftriaxone and who also developed abnormal gallbladder sonograms became symptomatic. Shortly after receiving dose 12 of ceftriaxone, patient 41 developed vomiting, which persisted for approximately 1 h. However, patient 41 completed the 14-day course of therapy, at which time the sonogram was interpreted as showing gallstones. Patient 38 experienced vomiting after dose 14 of ceftriaxone, at which time gallstones were diagnosed following ultrasound examination. No other patients in the study experienced vomiting.

Representative sequential photographs of the gallbladder abnormality observed in patient 38 are displayed in Fig. 1. The ultrasound characteristics of patients who developed apparent biliary pseudolithiasis are given in Table 3.

No significant differences in age, weight, duration of therapy, or dose were observed between patients who received ceftriaxone with and without the development of apparent biliary pseudolithiasis (Table 4). All patients who developed apparent biliary pseudolithiasis during ceftriaxone therapy were female ($P = 0.08$).

DISCUSSION

The development of sediment in the gallbladders of dogs and baboons that received ceftriaxone was first reported in 1981 (6). This finding appeared to be related to ceftriaxone dose, the length of ceftriaxone administration, or both. Chemical analysis of the sediment revealed a predominance of an insoluble calcium salt of the antibiotic.

In 1986, Schaad et al. (4) reported a case of an 18-year-old male who developed an abnormal gallbladder sonogram consistent with gallstones on serial examinations during ceftriaxone therapy. Ultrasonographic abnormalities normalized on the discontinuation of ceftriaxone. In 1988, another case report of ceftriaxone-associated cholecystitis was reported in a 16-year-old female (3). Again, follow-up ultrasound examination demonstrated marked improvement at 8 weeks postdischarge. Subsequently, Schaad et al. (5) prospectively evaluated serial abdominal ultrasonograms in 37 children who received ceftriaxone (60 to 100 mg/kg per day) for serious infections. Of 37 patients who were evaluated, 16 developed biliary concrements, with 3 patients developing symptoms. Sonographic abnormalities, symptoms, or both resolved 2 to 63 days following the discontinuation of ceftriaxone treatment.

Eight patients treated with ceftriaxone and with gallbladder sonograms interpreted as gallstones are known to have undergone cholecystectomy (unpublished data on file, Hoffmann-La Roche, Inc., 1989). One of these patients, an 85-year-old female, had true gallstones. Gallbladders of the remaining seven patients contained sandlike, semisolid particles and were reported as "not gallstones."

In this prospective randomized, double-blind, placebo-controlled trial, 21.4% (6 of 28) of adult patients who received ceftriaxone developed abnormalities on gallbladder ultrasound examination. In contrast, one of eight patients who received placebo developed abnormalities on ultrasound examination. Although the differences in the incidence of abnormal gallbladder sonograms in patients who received ceftriaxone and placebo were not statistically significant ($P = 0.491$), abnormalities were observed on ultrasound examination. The gallbladder abnormalities observed on ultrasound examination were interpreted as gallstones in five patients and as sludge in two patients (Table 3).

The findings in the eight unevaluable patients with abnormal sonograms at base line add to the complexity of this phenomenon. The two unevaluable patients who initially received placebo continued to have positive sonographic readings following placebo administration and were subsequently crossed over to receive ceftriaxone; after a full course of ceftriaxone, the sonogram in one patient was unchanged, while in the other the sonogram was interpreted as cleared. The remaining patients who were unevaluable received ceftriaxone initially, and no change was demon-

TABLE 3. Ultrasonographic characteristics of patients who developed apparent biliary pseudolithiasis

Patient no.	Treatment group	Radiologic image	Description of image	No.	Size (mm)
30	Ceftriaxone	Echo/shadow (stones)	Round/irregular	≥5	2–10
38	Ceftriaxone	Echo/shadow (stones)	Round	3	3
41	Ceftriaxone	Echo/shadow (stones)	Round/irregular	≥5	3–9
45	Ceftriaxone	Echo (sludge)	Linear particulate debris	>50	1–2
49	Ceftriaxone	Echo/shadow (stones)	Oval	≤3	2–7
54	Ceftriaxone	Echo/shadow (stone)	Oval	1	3
46	Placebo	Echo (sludge)	Linear particulate debris	>50	1–2

TABLE 4. Characteristics of patients who received ceftriaxone who did and did not develop apparent biliary pseudolithiasis[a]

Group (no.)	Age (yr)	Sex (M/F[b])	Wt (kg)	Treatment duration (days)	Dose (mg/kg per day)
With pseudolithiasis (6)	45.0 ± 12.3	0 M/6 F	61.7 ± 6.6	13.7 ± 0.8	32.7 ± 3.5
Without pseudolithiasis (22)	38.4 ± 15.4	8 M/14 F	69.7 ± 13.2	13.8 ± 0.8	26.9 ± 10.2

[a] Values are means ± standard deviations.
[b] M, Male; F, female.

strated in their sonographic findings after treatment. Therefore, in this small series of patients, ceftriaxone appeared to have no enhancing effect on the sonographic image in those patients with abnormal sonograms prior to therapy.

Ceftriaxone is extensively excreted into the bile (2; G. A. Gibson, P. R. Audet, G. Morrison, P. P. Soni, and I. H. Patel, Clin. Pharmacol. Ther. **43**:175, 1988). However, there is a large interpatient variation in absolute bile concentrations. Arvidsson et al. (1) observed a threefold interindividual variation in the biliary excretion of ceftriaxone. Furthermore, ceftriaxone biliary excretion has been correlated with the rate of bile acid secretion. If the mechanism of ceftriaxone-induced pseudolithiasis in humans is precipitation of the antibiotic in the gallbladder, individuals with increased bile acid secretion may be predisposed to the development of this adverse effect.

Because of its excellent antimicrobial spectrum of activity and attractive pharmacokinetic characteristics, ceftriaxone is used commonly in patients with serious bacterial infections. Apparent biliary pseudolithiasis may occur in patients who receive ceftriaxone. In our study, abnormal gallbladder sonograms in patients who received ceftriaxone were observed as echos with shadows (five of six patients) and were interpreted as gallstones. Furthermore, these abnormalities resolved spontaneously.

Awareness that sonographic interpretations of gallstone disease in patients who receive ceftriaxone may actually represent apparent biliary pseudolithiasis, a spontaneously reversible abnormality, will be conducive toward a conservative expectant approach to treatment with avoidance of surgery.

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