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Ceftriaxone Associated Biliary Sludge in Children - A Study in Bangabandhu Sheikh Mujib Medical University

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Abstract

Background: *Ceftriaxone is known to induce reversible precipitations, called billiary sludge or pseudolithiasis in the gall bladder.*

Objective: *The aim of this study was to investigate the frequency of biliary sludge and factors that contribute to this side effect in children.*

Methodology: *This study was conducted on 50 consecutive children who were admitted at paediatric department of Bangabandhu Sheikh Mujib Medical University (BSMMU) for different illness and who received ceftriaxone in different dosage and duration. Ultraso-nography of hepatobiliary system was done before and at the end of therapy. Children who developed biliary sludge, a third ultrasonography was done after one month.*

Results: *Biliary sludge was found in 4 (08%) of 50 children which resolved within 30 days of cessation of therapy. The mean dose and duration of ceftriaxone in these four children were 92.5±9.6 mg/kg/day and 8.0±2.0 days respectively while it was 78.5±5.2 mg/kg/day and 6.1±1.2 days respectively rest 46 children who did not develop biliary sludge ($p<0.05$). The mean age of children in sludge formation group was 8.3±2.1 years while it was 5.6±1.6 years in the normal group ($p<0.05$).*

Conclusion: *Biliary sludge was found in older children who got higher doses of ceftriaxone for a longer period and it was reversible in all the studied children.*

Key words: *Biliary sludge, ceftriaxone, ultrasonography.*

Introduction

Ceftriaxone is a sterile, semi-synthetic, broad-spectrum third generation antibiotic of cephalosporin group for intravenous and intramuscular administration. Thirty three to 67% of a ceftriaxone dose is excreted in the urine and the remainder in the bile[1]. Ceftriaxone is effective against a wide range of micro-organisms and rationally or irrationally it is being used in various clinical situations. Though safety and efficacy of ceftriaxone in paediatric practice is well established, sometimes it is associated with few side effects, biliary sludge formation is one of them (5-15%)[1]. Biliary sludge was first discovered in 1970s with the advent of ultrasonography (USG). Biliary sludge defined as a mixture of particulate matter and bile that occurs when various solutes in bile precipitate. It differs from small biliary stone which is a particle with a diameter of more than 2 mm and which can not be crushed by digital compression[2,3]. Apart from ceftriaxone therapy, biliary sludge may be associated with pregnancy, rapid weight loss, prolonged fasting, critical illness, and prolonged Total Parenteral Nutrition (TPN) therapy[4]. Ceftriaxone is a popular and frequently used antibiotic in our country. The present prospective hospital based analytic study was conducted to find out the frequency of biliary sludge formation in ceftriaxone treated children in a tertiary hospital and also to observe factors contributing to this and its fate.

Methodology

This study was conducted at the department of paediatrics, BSMMU, Dhaka from July 2006 through December 2006. For the study purpose 50 consecutive children of both sexes who were treated with ceftriaxone for various illness were enrolled in the study. Children getting another antibiotic in addition

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to ceftriaxone, having ultrasonographically proven gallstone/ biliary sludge at the beginning of therapy, suffering from liver diseases and children with hemolytic blood pictures were excluded from the study. Written informed consent was obtained from patients/ parents before enrollment of their names in the study. Diagnosis of the clinical condition was made by history, physical examinations and relevant investigations. In addition, LFTs and peripheral blood film study were done.

Ultrasonography of Hepatobiliary system were done before the initiation of treatment with ceftriaxone and also at the end of therapy to identify biliary sludge formation. A third USG was done after one month in those who developed biliary sludge to observe its fate. Ultrasonography were done by the same sonologist using the same machine (SIEMENS ACUSON, Antares Premium edition 2005) with appropriate transducer for children (3.5 and/or 5 MHz). Data were collected in a structured questionnaire. Significance of proportions was tested by calculating chi-square test and unpaired t test. The study protocol was approved by the departmental ethical committee of BSMMU.

Results:

The age range of the children was 2 months to 15 years (mean 6.2±3.9 years) and 33 (66%) were male. Thirteen (26%) of 50 cases were diagnosed as enteric fever and 12 (24%) nephrotic syndrome with infection (table-I). The mean duration of treatment with ceftriaxone was 9.9±2.6 days (range: 5-16 days). The dose of ceftriaxone varied from 50 to 100 mg/kg/day (mean 86.7±7.3 mg/kg/day). Only one child was kept nil per oral for 2 days with adequate hydration by IV fluid. Four (08%) of 50 children were found biliary sludge at the end of ceftriaxone therapy but repeat USG done after one month showed no biliary sludge in these 4 children. The mean dose and duration of ceftriaxone in these 4 children were 92.5±9.6 mg/kg/day and 8.0±2.0 days respectively (table II). On the other hand, it was 78.5±5.2 mg/kg/day and 6.1±1.2 days respectively in rest 46 children who did not develop biliary sludge at the end of ceftriaxone therapy. The mean differences of doses and duration were statistically significant ($p<0.05$). The mean age of children in sludge formation group was 8.3±2.1 years while it was 5.6±1.6 years in the normal group and this difference was also statistically significant ($p<0.05$).

Table-I

Clinical Diagnosis of the Cases (n=50).

Diagnosis	No	Percentage
Enteric fever	13	(26)
Nephrotic syndrome with infection	12	(24)
Chronic renal failure	06	(12)
Pneumonia with infection	03	(06)
Pulmonary TB with bronchiectasis	03	(06)
Neurocutaneous disease with ARI	02	(04)
Others	11	(22)

(Septicemia, paratyphod fever, rickettsia, lung abscess, posterior urethral valve with UTI, JIA with UTI, AV malformation with cellulites, meningitis, distal penile hypospadiasis with UTI, AGN with UTI, Kala azar with pneumonia)

Table II

Characteristic of patients with biliary sludge(n=04).

Parameters	Mean±SD
Age (years)	8.3±2.1
Weight (kg)	22.77.2
Dose of ceftriaxone (mg/kg/day)	92.5±9.6
Duration of ceftriaxone (days)	8.0±2.0

Table III

Characteristic of Normal and Biliary Sludge formation group(n=50).

Characteristics	Normal	Biliary sludge group	P value
No of patients	46(92.0)	4(8.0)	
Sex , M/F	31/15	2/2	> 0.05
Age (years)			
Mean ± SD	5.6±1.6	8.3±2.1	< 0.05
Range	2 mo – 15 years	16 mo – 15 years	
Weight (kg)			
Mean ± SD	21.9±6.5	22.7±7.2	> 0.05
Range	5 – 30	10 – 30	
Dose (mg/kg/day)			
Mean ± SD	78.5±5.2	92.5±9.6	< 0.05
Range	50 - 100	80 – 100	
Duration (days)			
Mean ± SD	6.1±1.2	8.0±2.0	< 0.05
Range	5 – 8	7 - 16	

Discussion:

Ceftriaxone is a semi-synthetic perenteral form of 3rd generation cephalosporin. It is a widely used broad spectrum antibiotic in paediatric practice due to its long plasma half-life and relatively low adverse effects. Schaad et al first observed biliary sludge after ceftriaxone therapy and since then many reports have been published[5-8]. Biliary sludge is a benign condition and symptoms like right upper quadrant pain, nausea, vomiting etc occur frequently[7,9,10].

The incidence of biliary sludge in ceftriaxone treated patients varies between 15 to 46%[7,11-13]. Schaad et al. found biliary sludge in 16 (43%) of 37 ceftriaxone treated children with only 3 (19%) of these 16 had symtoms[7]. Kong and Chen reported biliary sludge in 5 (3%) of 151 children receiving ceftriaxone at a dose of 50 mg/kg/day or more for 3 or more days another study on 118 children with ceftriaxone 100 mg/kg/day, 20 (17%) asymptomatic children developed biliary sludge[12]. A recent study[15] on 156 children, 11 (7%) showed biliary sludge which is almost consistent with the present study.

Variable dosage schedule and different duration of therapy may be the reasons of these variable results. Some study showed higher incidence due to co-administration of another antibiotics e.g. Flucloxacillin[7] while other showed higher incidence due to higher doses (100 mg/kg/day), restriction of oral intake and higher environmental temperature[16]. Biliary sludge usually develops between 3-22 days after beginning of ceftriaxone therapy[7,11]. In the present study biliary sludge developed after a mean period of 8 days (range: 7-16 days). The shortest interval of sludge formation was 2 days after initiation of therapy with ceftriaxone[10].

Biliary sludge is a reversible condition and usually disappears after a mean period of 15 days (range: 2-63 days) after discontinuation of therapy[7]. In the present study resolution of sludge was observed in all the cases within 30 days of cessation of therapy. The longest time interval i.e. 5 months of resolution of sludge was reported by Bonnet et al[13]. In the present study comparison was made between the biliary sludge formation group and normal group (Table-II). In normal group the mean dose of ceftriaxone was 78.5±5.2 mg/kg/day while in the biliary sludge formation group it was 92.5±9.6 mg/kg/day and this difference was statistically significant ($p<0.05$). Again the mean duration of ceftriaxone therapy in the normal group was 6.1±1.2 days while it was 8.0±2.0 days in the sludge formation group and this difference is also statistically significant ($p<0.05$). Older age was also found to be a risk factor for the development of biliary sludge in the study. The mean age of children in sludge formation group was 8.3±2.l years while it was 5.6±1.6 years in the normal group and the difference was also statistically significant ($p<0.05$).

Conclusion and recommendation

Ceftriaxone is a life saving and relatively safe antimicrobial agent for the treatment of serious bacterial infections in children but one of its unpleasant side effect is the formation of billiary sludge. The incidence of billiary sludge is higher in older children when received higher doses of ceftriaxone for longer duration. But the fate of that sludge is still under investigation and needs long term follow up. So, higher dose of ceftriaxone and its longer duration of treatment in children should be avoided whenever possible, in other cases alternative drug may be considered.

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