Ceftriaxone and Acute Renal Failure in Children

WHAT’S KNOWN ON THIS SUBJECT: Ceftriaxone at therapeutic doses can lead to renal stone formation.

WHAT THIS STUDY ADDS: Renal stone formation with ceftriaxone therapy can result in postrenal acute renal failure in children. The condition can be treated effectively by timely pharmacotherapy or retrograde ureteral catheterization with good prognosis.

abstract

OBJECTIVE: Our aim was to evaluate the clinical profile, treatment, and outcome of ceftriaxone-associated postrenal acute renal failure (PARF) in children.

METHODS: We retrospectively studied 31 consecutive cases from 2003 to 2012 for PARF after ceftriaxone treatment. There was no past history of urolithiasis or nephropathy in these children.

RESULTS: The average time of ceftriaxone administration before PARF was 5.2 days. The major symptoms apart from anuria included flank pain (>3 years old, 25/25), excessive crying (<3 years, 6/6), and vomiting (19/33). Ultrasound showed mild hydronephrosis (25/31) and ureteric calculi (11/31). Nine children recovered after 1 to 4 days of pharmacotherapy. Twenty-one children who were resistant to pharmacotherapy underwent retrograde ureteral catheterization. After catheterization of their ureters, normal urine flow was observed, and the symptoms subsided immediately. Catheter insertion failed in 1 child who subsequently underwent 3 sessions of hemodialysis before normal urination was restored. Ceftriaxone was verified to be the main component of the calculi in 4 children by tandem mass spectrometric analysis. The recovery was complete in all cases.

CONCLUSIONS: Ceftriaxone therapy in children may cause PARF. Early diagnosis and prompt pharmacological therapy are important in relieving the condition. Retrograde ureteral catheterization is an effective treatment of those who fail to respond to pharmacotherapy. Pediatrics 2014;133:e917–e922

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KEY WORDS
acure renal failure, child, ceftriaxone

ABBREVIATIONS
PARF—postrenal acute renal failure
RUC—retrograde ureteral catheterization
TMS—tandem mass spectrometric

Dr Li collected the data and wrote the article; Profs Zhou and Yuan performed the treatment of the children; Dr Chen and Prof Jiang carried out the ceftriaxone detection by mass spectrometric analysis; Prof Zhang conceptualized the article; and all authors approved the final manuscript as submitted.

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Ceftriaxone is a third-generation cephalosporin that is widely used to treat various infections during childhood. Long plasma half-life and single daily dose are the main advantages of this agent. Approximately 33% to 67% of ceftriaxone is excreted unmetabolized in the urine, whereas the remainder is excreted through biliary elimination. Clinical studies have demonstrated that ceftriaxone can cause biliary pseudolithiasis, nephrolithiasis, and bladder sludge, especially in children.

Ceftriaxone at therapeutic doses can lead to crystallization in the urine and these crystals adhere to the surface of renal tubular cells. Severe nephrolithiasis can cause postrenal acute renal failure (PARF). To date there are only a few studies reporting on PARF associated with ceftriaxone.

Our aim was to study the clinical features, treatment, and outcome of ceftriaxone-associated PARF in children.

METHODS
Between January 1, 2003 and June 30, 2012, of the 127 PARF children admitted to the Pediatric Surgery Department of Tongji Hospital, there were 31 children who had a history of ceftriaxone administration a few days before PARF. These children were identified as subjects for the study. The history of ceftriaxone treatment was verified from patient records in 9 children and reported by parents in the remaining 22 children.

The diagnosis of PARF was based on sudden onset of anuria, flank pain, and renal percussion pain associated with elevated serum creatinine and/or serum urea nitrogen in a child who had no past history of urolithiasis. The renal ultrasonography findings included normal-sized kidneys, the presence or absence of hydronephrosis, or ureteric calculi with no renal vascular abnormality or thrombus. The children who had known pre-renal causes of ARF, glomerulonephritis, or disorders that can cause renal injury such as autoimmune diseases, malignant hypertension, nephrotoxic drugs, rhabdomyolysis, or disseminated intravascular coagulation, etc., were excluded from the study. The medical records of these 31 children were retrospectively reviewed for the following data: primary disease for which ceftriaxone was administered; dose and time of ceftriaxone administration; time from the ceftriaxone administration to PARF; clinical manifestation of PARF; concomitant symptoms; renal ultrasound findings; tandem mass spectrometric (TMS) analysis of stones; treatment methods; and time taken for resolution of PARF. Prognosis data were also reviewed.

The beginning of PARF was considered to be from the last spontaneous voiding. Treatment time of PARF was considered to be from the beginning of treatment until the reflow of urine (at a rate of >0.5 mL/kg/h).

The therapeutic principle adopted included initiation of pharmacotherapy and, if the children showed no sign of urination until serum creatinine exceeded 500 μmol/L, treatment with retrograde ureteral catheterization (RUC) was performed. In cases in which both methods failed, hemodialysis was used. Nephrostomy was considered as the last option. Parents were told to follow-up at least 1 month after discharge.

Pharmacotherapy included spasmolysis (anisodamine), alkalinization (sodium bicarbonate), antibiotics, albumin supplement, and low doses of dexamethasone. Total liquid intake was strictly controlled and monitored. Potassium supplementation was not used unless polyuria stage was reached. Serum creatinine, blood potassium, blood pressure, and evidence for pulmonary edema were monitored accordingly.

RESULTS
Baseline Characteristics, Primary Diseases, and Ceftriaxone Administration
Among the 31 cases of ceftriaxone-associated PARF, 25 were boys and 8 were girls. The mean age was 5.1 years (range, 1–12 years). The primary diseases for which ceftriaxone was administered included 12 cases of pneumonia, 5 cases of upper respiratory tract infections, 5 cases of sinusitis, 1 case each of meningitis, parotitis, and left arm trauma, and 6 postoperative cases (3 for hypospadias, 2 for appendicitis, and 1 for femoral fracture). Family histories revealed a history of urolithiasis in parents of 3 cases. None of the siblings had urinary calculi.

The average time of ceftriaxone administration was 5.2 days (range, 3–7 days). The exact doses of ceftriaxone administration were available in 13 cases and ranged from 70 to 100 mg/kg/d (mean, 86.7 mg/kg/d). The average time from the first day of ceftriaxone administration to anuria was 5.4 days (range, 3–9 days).

Clinical Features
The clinical symptoms included a sudden onset of anuria for at least 24 hours (31/31), flank pain (>3 years old, 25/25; 17 bilateral and 8 unilateral), excessive crying (<3 years, 6/6), and nausea and/or vomiting (19/31). Nine children had mild dehydration and 5 were edematous. Severe dehydration was not recorded in any case.

Renal ultrasonography revealed bilateral mild hydronephrosis in 6 children and unilateral mild hydronephrosis in 19 children. Six children had normal renal ultrasonographs. The average anteroposterior diameter of the pelvis
was 0.64 cm (range, 0.4–1.2 cm). Ureteric calculi were found in 11 children. The diameters of calculi ranged from 0.2 to 0.6 cm (mean, 0.3 cm). Biliary ultrasonography was performed in 22 children, among which 4 were found to have biliary pseudolithiasis. Abdominal radiographs showed fluid levels in 3 cases and no calculus was observed in any of the patients (Table 1).

Treatment and Effectiveness

Nine patients began to urinate and recovered after 1 to 4 days of pharmacotherapy.

Twenty-one children who were resistant to pharmacotherapy and had serum creatinine >500 μmol/L required RUC by cystoscopy. Five children had serum creatinine levels above 500 μmol/L at the time of admission. Sixteen children (mean age, 4.4 ± 2.0 years) underwent bilateral RUC, and 5 children (mean age, 8.2 ± 2.9 years) underwent unilateral RUC. Unilateral RUC was used in these 5 children as only 1 side could be catheterized; a catheter could not be inserted into the other side owing to an edema of the ureterovesical orifice and calculi blockage. These 5 children were also significantly older than the other 16 children (P < .01). Once the catheters were in situ, normal urination returned and the situation improved accordingly in children who underwent bilateral and unilateral catheterization. The catheters were removed after 3 to 5 days.

RUC failed on both sides in 1 patient, a 10-year-old boy, owing to dense calculi blocking the ureteric orifices. After several attempts to catheterize the patient, the orifices of the ureter became edematous and started to bleed. This child was referred for hemodialysis. After 3 sessions of hemodialysis on alternative days, normal urination was re-established.

The mean treatment duration was 1.8 days (range, 1–7 days). The mean anuria period was 3.1 days (range, 1–8 days). No nephrostomy was performed in any of the cases. The serum creatinine and serum urea nitrogen decreased rapidly after urination returned. Urinalysis of samples collected soon after recovery varied widely. Most children had red blood cells and white blood cells in the urine, especially those who underwent RUC. Proteinuria was mild or absent. Hyaline and granular casts were observed in a few patients. Subsequent urinalysis 1 to 5 days later revealed normal findings except for a few white blood cells in a few cases. The ultrasonography findings did not help to choose the modality of treatment, whether conservative line or ureteral catheterization.

All children were cured and discharged. Twenty-three children were followed over the next 4 weeks. No sign of relapse was observed. Ultrasound scans, performed 1 month post-discharge, showed no signs of stones. Four children had mild hydronephrosis and required further follow-up with regular ultrasound examination.

TMS Analysis

Because of its sand-like structure, most of the calculi were flushed away during the catheterization. We could only collect 6 samples of urinary calculi and in 4 of them ceftriaxone was confirmed to be the main component of the calculi by TMS (Fig 1). The other 2 samples were too heavily contaminated with red blood cell fragments to be of any value for analysis.

DISCUSSION

Several studies have shown ceftriaxone to cause biliary pseudolithiasis and nephrolithiasis. However, ceftriaxone-associated PARF has been rarely reported. In this study we identified 31 children who had PARF who had a definite history of ceftriaxone treatment demonstrating the causal role of ceftriaxone in PARF.

Ceftriaxone at therapeutic doses can crystalize with calcium in the urine and adhere to the surface of renal tubular cells. It can even increase urinary calcium excretion. Thus ceftriaxone, by increasing the excretion of urinary calcium and crystallizing with calcium, forms stones that obstruct the ureters, resulting in PARF. In addition, the “reflex anuria” mechanism also contributes to this situation. We observed through the use of ultrasonography that the majority of cases (25/31) had no detectable abnormality at least in 1 kidney. In 5 cases, unilateral RUC resolved the anuria, and when unilateral ureter drainage was established the contralateral obstruction improved immediately whether the contralateral side had hydronephrosis or ureteric calculi. These observations support the reflex anuria mechanism. The obstruction of the ureter on 1 side by ceftriaxone crystals led to reflex anuria on the other side, resulting in PARF. However the exact mechanism of reflex anuria is still unknown. Dehydration may be an important inducing factor. Most of the children in this series were reluctant to drink much water after the primary disease, which may have exacerbated the pathogenesis.

Although ultrasonography is a highly specific modality in PARF diagnosis, not all PARF patients show positive results. Six children in the current study did not show abnormalities in renal sonography. Sudden and complete anuria in these children with no contributing history or specific laboratory findings for other causes led us to confirm PARF in these children. Generally the ceftriaxone renal stones are small, remain asymptomatic, and do not need any specific treatment. After cessation of ceftriaxone therapy, the stones vanish by themselves.
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this view, we initiated pharmacotherapy for all children upon diagnosis, and 9 children responded well. In the other children, the ceftriaxone stones were found to be more compact and obstructed the urinary tract. Their ureteral orifices had inflammatory swelling under cystoscopy, which might have aggravated the obstruction. Pharmacotherapy aimed to dilate the ureters and relieve spasm (anisodamine), relieve edema of the renal pelvis and ureter (albumin and low dose of dexamethasone), and most importantly, prevent complications such as acidosis (sodium bicarbonate) and urinary tract infections (antibiotics). Once the ceftriaxone administration is stopped, swelling of the ureteral orifices subsides, and stones get expelled, thus relieving the symptoms. The pharmacotherapy helps to maintain the homeostasis during this waiting period. Through pharmacotherapy alone, 9 children in this study recovered by days 1 to 4. Theoretically, pharmacotherapy can be continued as long as the water-electrolyte and acid-base balance is not severely disturbed. In this study, the longest pharmacotherapy lasted 4 days.

Acute pulmonary edema resulting from fluid retention and cardiac arrest resulting from hyperkalemia are 2 of the most lethal complications of PARF. For this reason we paid special attention to restriction of fluids and avoided potassium supplements until the polyuria stage. Through these measures neither pulmonary edema nor hyperkalemia was observed. The earliest and most prominent abnormality in routine blood tests that was observed was increasing creatinine levels. We set the serum creatinine to a level not to exceed 500 μmol/L, above which catheterization was performed. For those patients who showed no sign of recovery after pharmacotherapy and increasing serum creatinine levels beyond 500 μmol/L, RUC was performed. Viewed through the cystoscope, the ceftriaxone calculi appeared as sand grains. Because of the sand-grain nature of this calculi, ultrasonic lithotripsy, holmium laser lithotripsy, or lithotomy do not render any help. In the majority of cases the catheters could be inserted into the blocked ureters without much difficulty. Through catheterization alone the stones could be flushed out in some instances. In a few cases, however, the stones were more compact, which made it difficult to insert the catheters. The catheterization failed often in older children. All children younger than 4 years had easy catheterization. The mean age of the 5 children in whom catheterization failed on 1 side was 8.2 years. Bilateral catheterization of the ureter failed on both sides in 1 patient, a 10-year-old child. It appears that more and stable crystallization is needed to obstruct the urinary tract in older children. Hence, the stone formation is lower in older children, but once it forms, the stones are usually more compact.

All children in this study had a good post-treatment prognosis. Four children were found to have mild hydronephrosis after 1 month. This might be because the hydronephrosis caused by the obstruction had not yet recovered. The other reason could be previous existence of other urinary abnormalities, such as ureteropelvic junction obstruction, which increases the risk for nephrolithiasis.16 No other significant sequelae were observed in any case. These results indicate that ceftriaxone-associated PARF is reversible and has a good prognosis if prompt and proper treatments are administered in time.

The limitations of the current study include small sample size and retrospective design. The non-availability of

**FIGURE 1**
Stone analysis by TMS. Urinary sediment samples from a patient were washed and dissolved in 1% formic acid solution. Ceftriaxone calcium dissolved in 1% formic acid solution was used as a positive control. AB Sciex 4000 Q-Trap instrument was used for TMS analysis. The Q1 scan showed ceftriaxone parent ion with mass charge ratio 553.0 in both A, control and C, patient sample. Product ion scans further showed that in the B, control and D, patient sample, the fragment ions (fragment of ceftriaxone) were similar. Cps, counts per second; Da, dalton; m/z, mass charge ratio.
exact doses of ceftriaxone in all cases is another limitation. TMS analysis of stones confirmed ceftriaxone as the main component of the calculi in only 4 patients. The sand-grain nature of ceftriaxone stones makes it difficult to collect. This particular limitation of the study stresses the need for an improved technique for the collection and analysis of these calculi in future studies.

Based on the current data it is difficult to estimate the incidence of PARF in all ceftriaxone-treated children. We presume that it is low. If anuria or flank pain is observed in children receiving ceftriaxone treatment, therapy should be stopped immediately and such children should be investigated by using the relevant blood tests and renal ultrasonography. If PARF is confirmed, then the drug should be stopped and proper therapy for PARF should be initiated at the earliest.

CONCLUSIONS

This retrospective study showed that ceftriaxone therapy could lead to PARF. In ceftriaxone-associated PARF, conservative pharmacotherapy is helpful, but when it fails, RUC is an effective therapeutic option.

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