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.

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
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 (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 dexmethasone. 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, 23 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, 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 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.

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**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 crystallize 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 crystalizing 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. With
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this view, we initiated pharmacother-
apy 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 ori-
fi
ces had in
fl
ammatory
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 ori-
fi
ces subsides, and stones get expelled,
thus relieving the symptoms. The
pharmacotherapy helps to maintain
the homeostasis during this waiting
period. Through pharmacotherapy use
alone, 9 children in this study recovered
by days 1 to 4. Theoretically, pharma-
cotherapy can be continued as long as
the water-electrolyte and acid-base
balance is not severely disturbed. In
this study, the longest pharmacother-
apy 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 atten-
tion to restriction of fluids and avoided
potassium supplements until the poly-
uria stage. Through these measures
neither pulmonary edema nor hyper-
kalemia was observed. The earliest and
most prominent abnormality in routine
blood tests that was observed was in-
creasing creatinine levels. We set the
serum creatinine to a level not to exceed
500 μmol/L, above which catheteriza-
tion was performed.

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.

and increasing serum creatinine levels
beyond 500 μmol/L, RUC was per-
formed. Viewed through the cysto-
scope, 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 diffi-
culty. Through catheterization alone
the stones could be flushed out in
some instances. In a few cases, how-
ever, 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 cath-
erization. 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 chil-
dren were found to have mild hydro-
nephrosis 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 abnormali-
ties, such as ureteropelvic junction
obstruction, which increases the risk
for nephrolithiasis.16 No other signi-
fi
cant sequelae were observed in any
case. These results indicate that
ceftriaxone-associated PARF is re-
versible 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 retro-
spective design. The non-availability of
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.

REFERENCES

Ceftriaxone and Acute Renal Failure in Children
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