

KIDNEY STONES AND CEFTRIAXONE

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ABSTRACT

Metabolic causes such as hypercalciuria, urinary tract infection, and obstruction are the most common aetiologies of urolithiasis, and drugs, although important in this regard, are rarely the cause of urolithiasis. Administration of one of these drugs, ceftriaxone (CTX), has been associated with biliary pseudolithiasis in adult and paediatric patients, and rarely may cause urolithiasis. Several factors, including drug concentration and incubation time, are very important for determining the degree of CTX/calcium (Ca) crystallisation in the urine. According to this data, CTX crystallisation was a dose and time-dependent reaction. It is particularly important to monitor patients on high-dose long-term CTX treatment with the urinary Ca to creatinine ratios, ultrasound sonography, and renal function testing, as these individuals may be at greater risk of large stones and renal damage. This type of screening may help prevent permanent complications in the future. This underlying review will help to educate readers on the pathophysiology and interaction between CTX and urolithiasis.

Keywords: Ceftriaxone, urolithiasis.

INTRODUCTION

The prevalence of urolithiasis requiring medical or surgical treatment is 5-10% and increasing worldwide.¹ Calcium (Ca) oxalate is the most prevalent type of kidney stone disease in the United States and has been shown to occur in 70-80% of the kidney stone population.² The prevalence of recurrent Ca oxalate stones has progressively increased in untreated subjects, approaching a 50% recurrence rate over 10 years.³ The lifetime risk for kidney stone disease currently exceeds 6-12% in the general population.⁴ In the final quarter of the twentieth century, the prevalence of kidney stone disease increased in both males and females, and all ethnicities.⁴

Metabolic causes such as hypercalciuria, urinary tract infection (UTI), and obstruction are the most common aetiologies of urolithiasis, and drugs, although important in this regard, are rarely the cause of urolithiasis. Drugs may be responsible for 1-2% of all renal calculi.⁵ This drug adverse event most often affects patients who have received high-dose and/or long-term treatment of some

drugs with lithogenic potential.⁵ According to mechanisms of calculi formation, lithogenic drugs can be classified into two groups.⁵ The first group consists of drugs that induce metabolic abnormalities (e.g. hypercalciuria,^{6,7} hypocitraturia,^{8,9} hyperuricosuria,¹⁰ and alteration of urine acidity^{8,9}) which subsequently provoke formation of metabolic calculi; e.g. Ca-containing stones and uric acid (UA) nephrolithiasis.⁵ The second group consists of drugs that can be crystallised directly in the urine due to their high excretory levels and poor solubility.¹¹⁻¹⁴ The most important drugs are silica-containing anti-acids, furosemide, acetazolamide, ciprofloxacin, sulfonamides, aminophylline, corticosteroids, triamterene, phenytoin, probenecid, lithium, indinavir, and ceftriaxone (CTX).¹⁵ Administration of one of these drugs, CTX, has been associated with biliary pseudolithiasis in adult and paediatric patients, and rarely may cause urolithiasis.^{16,17} Although only limited information exists in the literature regarding the incidence of urolithiasis following CTX therapy, the present review is aimed to demonstrate interaction between CTX and urolithiasis.

Up to 75% of stones are Ca oxalate, the others are struvite (magnesium ammonium [NH] phosphate, 10–20%), UA (5%), 5% contain >50% brushite (Ca monohydrogen phosphate) or hydroxyapatite, and <1% are composed of cystine.¹⁸ Although much progress has been made in understanding the pathophysiological mechanisms of stone disease, allowing for more effective diagnosis and treatment, stones still cause substantial morbidity from pain, urinary-tract obstruction, and infection.¹⁹

A. Ca Stones

Hypercalciuria, the most common metabolic abnormality found in patients with recurrent Ca stones, is most often familial and idiopathic²⁰ and is strongly influenced by diet. Gut Ca absorption is increased in persons with idiopathic hypercalciuria, but serum Ca values remain unchanged, since absorbed Ca is promptly excreted.²¹ On a low-Ca diet, such persons often excrete more Ca than they eat,²² and urinary Ca excretion also rises markedly after the intake of Ca-free nutrients such as simple oral glucose; in such cases, the only source possible is bone. Although hypercalciuria is sometimes divided into subtypes (absorptive, resorptive, and renal leak), this classification is not helpful in guiding treatment. However, measurement of serum Ca is indicated to identify patients with primary hyperparathyroidism. Primary hyperparathyroidism, which results from an adenoma in 85% of cases, is associated with mild-to-moderate hypercalcaemia. Hypercalciuria is a result of excess parathyroid hormone, which causes overproduction of 1.25-dihydroxyvitamin D in the kidney; both factors promote bone resorption, increasing the filtered load of Ca and hence calciuria. Other disorders that induce hypercalcaemia can also result in hypercalciuria: malignancies, granulomatous diseases, sarcoidosis, thyrotoxicosis, and immobilisation. Idiopathic hypercalciuria is a familial disorder affecting both sexes equally, in which urinary Ca concentration is raised despite normal concentrations of blood Ca.^{23,24}

The level of oxalate excretion is modestly higher among patients with recurrent Ca stones than among those without the condition. The human serum oxalate concentration ranges between 1 and 5 mm, however, due to water reabsorption in the kidney, its concentration is 100-times higher in

the urine. At a physiologic pH, oxalate will form an insoluble salt with Ca. As the solubility of Ca oxalate in an aqueous solution is limited to approximately 5 mg/l at a pH of 7.0, assuming that normal urine volume ranges between 1 and 2 l/day and normal urinary oxalate excretion is <40 mg/day, normal urine is often supersaturated with Ca oxalate. However, under normal conditions, the blood is undersaturated in respect with Ca oxalate. As seen in patients with primary hyperoxaluria and renal insufficiency, when the serum oxalate concentration increases to above 30 μ M, the blood becomes supersaturated with Ca oxalate. In the plasma, oxalate is not significantly bound to protein and is freely filtered by the kidneys. A recent study reported that urinary Ca is as important as urinary oxalate in raising Ca oxalate supersaturation.^{24,25} Finally, citrate chelates Ca in the urine, decreasing supersaturation and reducing the growth of crystals; hypocitraturia is a risk factor for stone formation.²⁶ Hypocitraturia could result from causes of intracellular acidosis such as renal failure, potassium deficiency, distal renal tubular acidosis, chronic diarrhoeal states, and drugs such as acetazolamide. Many patients with stones have unexplained low urinary citrate; dysfunction of the renal sodium-citrate cotransporter has been proposed as a possible mechanism.²⁷

B. UA Stones

Three major factors for the development of UA stones are low urine volume, acidic urine pH, and hyperuricosuria. The aetiologic mechanisms for UA stone formation are diverse and include congenital, acquired, and idiopathic causes. The most prevalent cause of UA nephrolithiasis is idiopathic. Diets high in purines, especially those containing organ meats and fish, result in hyperuricosuria, and, in combination with low urine volume and low urinary pH (as a result of impaired renal ammonia production), can exacerbate UA stone formation. Furthermore, hyperuricaemic disorders including gout (about 20% of patients with gout are hyperuricosuric), myeloproliferative disorders, tumour lysis syndrome, and inborn errors of metabolism (such as Lesch-Nyhan syndrome and glucose-6-phosphatase deficiency) result in an increased filtered load of UA and thus, hyperuricosuria.²⁸

The metabolic defect suspected for low urinary pH in UA stone formation was described almost four decades ago. Defective ammoniogenesis or excretion was attributed as a possible pathogenetic

mechanism. Initial studies showing abnormalities in glutamine metabolism, which resulted in the impaired conversion of glutamine to α -ketoglutarate and consequently resulted in reduced renal NH excretion, were not supported by further investigation.²⁹ Mechanistic studies, however, have shown that the two major factors responsible for abnormally low urine pH are a combination of defective NH excretion and increased net acid excretion.

C. Struvite (Magnesium NH Phosphate) Stones

Struvite stones are associated with chronic UTI with Gram-negative rods capable of splitting urea into NH, which combines with phosphate and magnesium. Usual organisms include *Proteus*, *Pseudomonas*, and *Klebsiella* species. *Escherichia coli* is not capable of splitting urea and, therefore, is not associated with struvite stones. Urine pH is typically >7. UTI does not resolve until the stone is removed entirely.²⁴

DRUG-INDUCED UROLITHIASIS

Drug-induced renal calculi (kidney stones) represent 1-2% of the total number of renal calculi analysed in specialised laboratories. Historically, sulfonamides were the first drugs implicated in renal calculi formation and acute renal failure (ARF) episodes early after their use in humans. A number of reports were published on sulfonamides and renal disorders.³⁰⁻³⁴ Two main mechanisms are involved in the formation of drug-induced renal calculi: (i) the drug and/or its metabolites are total or partial components of the calculi; and (ii) the drug induces the formation of calculi through its metabolic action by interfering with Ca oxalate or purine metabolism.³⁵⁻³⁷ In both cases, alithogenic substance may deposit on renal calculi already present. Therefore, patients with a history or presence of renal calculi seem to be more exposed to the risk of drug-induced renal calculi, and in our previous study we reported that urolithiasis risk is higher in patients who have urolithiasis.¹⁷ Obviously, only a limited proportion of patients treated with widely used drugs such as triamterene or sulfonamides develop crystalluria, renal colic, or ARF due to tubular obstruction by drug crystals. This suggests that the formation of drug-induced calculi involves an interplay of risk factors specific for the implicated drug, some of which depend on the drug itself and others that relate to the patient.³⁶⁻³⁸

The true prevalence of drug-induced renal calculi is likely to be underestimated in most studies. However, in some cases, changes in urine biochemistry induced by the drug may provoke crystallisation of metabolic compounds with an unusual morphology, which may draw attention to the possibility that there are peculiar conditions for the renal calculi formation.³⁹ The first large-scale epidemiological study of drug-induced nephrolithiasis was presented in 1980 by Ettinger et al.⁴⁰ The authors reported that 0.4% of 50,000 renal calculi analysed over a 6-month period in the United States contained triamterene, but they did not provide data as to the possible other types of drug-induced calculi. In 1986, Asper⁴¹ observed an incidence of 0.1% for drug-containing urinary calculi among a series of 14,165 calculi analysed between 1982 and 1985 in Switzerland.

CTX

CTX is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. The chemical formula of CTX sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59. CTX is a widely-used, third-generation, semisynthetic cephalosporin commonly administered for the treatment of different bacterial infections. Due to its broad spectrum against bacteria, long half-life (7-8 hours), and single daily dosing, physicians prefer to use it more frequently.⁴² CTX is used to treat a wide variety of serious infections caused by organisms that are resistant to most other antibiotics. It is often used (in combination, but not direct, with macrolide and/or aminoglycoside antibiotics) for the treatment of community-acquired or mild-to-moderate healthcare-associated pneumonia. It is also a choice drug for the treatment of bacterial meningitis caused by pneumococci, meningococci, *Haemophilus influenzae*, and susceptible enteric Gram-negative rods, but not *Listeria monocytogenes*.⁴³ Other uses included the treatment of acute bacterial otitis media, skin and skin structure infections, bone and joint infections, gonorrhoea, intra-abdominal and UTIs, pelvic inflammatory disease (PID), and bacterial septicaemia. It is also approved to be used in surgical (perioperative) prophylaxis.

Like other third-generation cephalosporins, CTX is active against citrobacter, *Serratia marcescens*, and β -lactamase-producing strains of haemophilus and neisseria. However, unlike ceftazidime and

cefoperazone, CTX does not have useful activity against *Pseudomonas aeruginosa*. It is not generally active against enterobacter species, and its use should be avoided in the treatment of enterobacter infections even if the isolate appears susceptible because of the emergence of resistance. Like all other cephalosporins, it has no activity against enterococci, atypicals (mycoplasma and chlamydia), or *Listeria*.⁴⁴ CTX can be administered intravenously and intramuscularly. It is not available orally. For most infections, CTX can be injected once every 24 hours at a dosage of 15-50 mg/kg/d. A single daily 1 g dose is usually sufficient. A dose of 2 g every 12 hours is recommended for the treatment of meningitis. A single intramuscular dose of 250 mg is recommended for the treatment of gonorrheal urethritis and cervicitis in conjunction with a single 1 g oral dose of azithromycin or doxycycline 100 mg orally twice daily for 7 days to cover chlamydia co-infection.⁴⁵ CTX is mostly eliminated through the kidney and the remainder is eliminated via the biliary system. Its concentration in bile is 20-150-times more than in plasma. It binds with Ca ions producing reversible precipitations that form biliary sludge and/or lithiasis, called pseudolithiasis both in children and adults.^{44,46-51}

CTX Induced Urolithiasis

CTX is filtered by the kidneys unchanged and forms insoluble salts with Ca in a 1:1 molar ratio. Risk factors for urolithiasis are not well-established but certainly poor urine output, high doses of CTX, and hypercalciuria may favour CTX-induced nephrolithiasis. Stojanovic and Djuric Vijatov⁵² reported a paediatric patient who developed nephrolithiasis in a kidney with congenital ureteropelvic junction obstruction.

CTX-induced urinary precipitates may be asymptomatic and detected on routine ultrasound (US) scanning but in some patients they may manifest haematuria or renal colic.^{47,53-59} Bilateral obstruction with calculi may lead to ARF in the patient as reported by Prince and Senac.⁵³ Also, Zhao-Lun Li et al.⁶⁰ presented the development of bilateral distal ureteral CTX-associated lithiasis in seven adults. The risk of ureterolithiasis impaction should be considered when treating patients with CTX, even in adults. When using high-dose and long-term CTX, avoiding simultaneous administration of Ca-containing liquid, more aggressive hydration and close clinical observation for urine crystalluria were recommended, especially in children and patients under fasting or post-

operative conditions. Often there is coexistence with biliary pseudolithiasis, and confusion may arise in a child with pain in the right upper abdominal quadrant during CTX treatment.⁵⁴ Thus, besides examination of the gall bladder, careful US scanning of the kidney and urine analysis should be performed.

The true prevalence of CTX-induced nephrolithiasis is not known. The first case of CTX-induced nephrolithiasis was reported by Schaad et al. in 1988.⁶¹ In their series of 37 children treated with CTX, 16 developed biliary pseudolithiasis and 1 child had concurrent biliary and urinary calculi, manifesting renal colic and obstruction of the kidney. In the recent prospective study by Biner et al.⁴⁷ 156 children with various infections treated with CTX at the doses of 50 mg/kg, 75 mg/kg, and 100 mg/kg have been followed by US scan. 27 children (17%) developed biliary pseudolithiasis or sludge, while only 1 child (0.6%) had urolithiasis. Mohkam et al.⁵⁸ prospectively followed 284 children with pyelonephritis (185 girls and 99 boys). Nephrolithiasis was identified in four children (1.4%). None of the children had a metabolic risk factor.

The results in a present study clearly demonstrated that CTX at therapeutic urinary excretion levels could directly interact with free Ca at physiologic urinary concentration to generate CTX/Ca crystals.⁶² Several factors, including drug concentration and incubation time, are very important for determining the degree of CTX/Ca crystallisation. According to these data, CTX crystallisation was a dose and time-dependent reaction. Therefore, high-dose CTX administration (which leads to increasing urinary CTX levels) and urinary stasis by any causes (which leads to retention of CTX crystals in the urinary tract, allowing crystal growth and aggregation) may aggravate CTX calculi formation. In summary, this present study has shown that CTX could be crystallised in the urine under physiologic conditions. The size of CTX crystal aggregates was much larger than the diameter of renal tubular lumens, implicating that tubular occlusion may be the major mechanism for subsequent development of CTX calculi. In addition, crystal adhesion onto the renal tubular cell surface may also play an important role in the initiation of CTX-induced nephrolithiasis. The findings of this study showed that CTX crystals could tightly adhere to the renal tubular cell surface, suggesting the high adhesive force between CTX crystals and renal tubular cell surfaces. Although the mechanism for such crystal-cell adhesion is still

unknown, one possibility is that CTX/Ca crystals may adhere onto the cell surface via ionic interaction and/or hydrogen bond, similar to other Ca-containing crystals (e.g. Ca oxalate, Ca phosphate). Another possibility is that Madin-Darby canine kidney cell surface may present some (unknown) receptors for CTX crystals. These hypotheses should be further elucidated.

By studying the effect of human physiological urinary pH on CTX-induced crystallisation, Cong et al.⁶³ showed more acidified urine could inhibit more CTX-induced crystallisation when urinary pH is <5.5. This study also suggests that alkaline urine predisposes CTX-induced crystallisation. Among very limited reports of CTX-induced nephrolithiasis with compositional analysis, Gargollo et al.⁶⁴ reported that CTX-induced stones were composed of CTX and Ca phosphate. As we know, Ca phosphate stones are usually formed in alkaline urine.⁶⁵ In this study, Cong et al.⁶³ also demonstrated that citrate is a potent inhibitor of CTX-induced crystallisation as well as its role against Ca oxalate and phosphate stones. Therefore, hypocitraturia should predispose CTX-induced nephrolithiasis. It is well known that UTI is often associated with the decreased urinary citrate concentration because a number of bacteria use citrate for their metabolism, resulting in hypocitraturia.⁶⁶ Therefore, patients with UTIs treated by CTX probably favour CTX-induced nephrolithiasis.

In our study published recently, we assessed the adult patients and found that after the CTX therapy 24-hour urine Ca excretion was higher than before the therapy.¹⁷ It is possible that the reaction and subsequent precipitation of CTRX with Ca within renal tubules lead to the disturbance of tubular reabsorption of Ca, resulting in excessive urinary excretion. It has been reported that >95% of the Ca filtered from the blood into urine is reabsorbed in the renal tubules under physiological conditions, with approximately 70%

of the Ca being absorbed in the proximal tubules, about 20-30% being reabsorbed in the loop of Henle, 5-10% being reabsorbed in the distal tubules, and the remaining (5%) Ca present in the renal collecting duct.⁶⁷ In contrast to the distal tubules, where Ca is reabsorbed actively by parathyroid hormone, Ca is passively reabsorbed by way of paracellular diffusion mediated by convection (solvent drag) across the tight junction in the proximal tubules. In conjunction with the findings in our study that there were no significant changes in serum Ca concentration, which mainly regulates parathyroid hormone, it seems reasonable to speculate that CTRX in urine prevents passive paracellular reabsorption of Ca in the proximal tubule, leading to excessive excretion of Ca and resulting in precipitation via the formation of an insoluble salt.

CONCLUSION

CTX can significantly increase the urinary excretion of Ca in adults, especially in those who have urolithiasis. Physicians should be aware of this side-effect and pay attention to the patient's hydration status and encourage mobilisation during cephalosporin treatment. Ampicillin may be preferred for prophylactic use of antibiotics because it does not escalate urinary excretion of Ca in stone patients. It is particularly important to monitor patients on high-dose long-term CTX treatment with the urinary Ca to creatinine ratios, US sonography, and renal function testing, as these individuals may be at greater risk for large stones and renal damage. This type of screening may help prevent permanent complications in the future. CTX urolithiasis was self-limited without long-term complications in all patients, and the use of this effective drug can be safely continued. We recommend close monitoring of CTX-treated patients with regards to possible kidney stone formation.

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