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Urine saturation and promoter/inhibitor parameters and ratios in renal stone disease caused by ceftriaxone

Case Report

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Abstract: During ceftriaxone treatment of subdural empyema caused by Streptococcus intermedius urinary and biliary stones were noticed. Increased levels of urinary calcium excretion were detected during ongoing treatment in comparison with 2 months check-up. There were no significant changes in the promoter/inhibitor urolithiasis parameters, oxalate, citrate, urate, cistine, glycosaminoglycans or their ratios. Urine saturation was calculated using EQUIL 2 computer programme (calcium oxalate, brushite) and it was normal. Probable trigger for the ceftriaxone/calcium hydroxy carbonate phosphate mixture of stones was a critical boost of solubility products caused by ceftriaxone treatment and phospnate urine content with a subsequent large-scale spontaneous precipitation of crystals.

Keywords: *Ceftriaxone • Urolythiasis • Urine saturation • Stone promoters/inhibitors*

1. Introduction

More than two decades have passed since the first article about ceftriaxone biliary stones was published [1]. Contrary to biliary pseudolithiasis caused by cephtriaxone treatment, the pathogenesis of urinary stones of the same origin has still remained far less satisfactorily explained [2-7]. Some investigations point to possible association with increased urinary calcium excretion, although majority of reports declare unclear results. We describe a case of a boy with gallblader and urinary stones of ceftriaxone composition, ensued during subdural empyema antibacterial therapy [8-10].

2. Patients and methods

A boy aged 11 years was treated for subdural empyema caused by Streptococcus intermedius with ceftriaxone (100 mg/kg/24-h for 13 days) determined by repeated blood cultures sensitive to ceftriaxone and Penicillin G. During treatment sponteneous passage of renal stones was noticed and therefore ceftriaxone medication was immedeately withrowan. The ultrasound of kidney and abdomen revealed numerous stone formations in both pyelocaliceal systems and the gallbladder. performed infrared (IR) spectroscopy analysis of passed kidney stones to asses any existing predisposition to urinary

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stone disease. Urinary calcium, oxalate, citrate, urate, cistine and glycosaminoglycans, as well as plasma and urine electrolytes and acid-base balance parameters were determined. The risk of stone formations was calculated by the promoter/inhibitor of individual parameters and its ratios [11,12]. Urine saturation was calculated using EQUIL213. For this purpose we obtained 24-h urine collections and analysis were performed over 2 consecutive days and on the third day one urine sample was collected between 8 to 10AM. The 24-h urine from the first day served for measuring creatinine, calcium, sodium, potassium, oxalate, phosphate, magnesium, citrate and sulphate. Sample was collected in a wide-mouth plastic bottle containing 10 ml of 6N hydrochloric acid, as a preservative. The 24-h urine from the second day was collected in the same way, but without addition of hydrochloric acid to the bottle. This sample was used for measuring chloride, urate, glycosaminglycans and creatinine. Sample from the third day (2h) was used for measuring ammonium and creatinine. To this sample 500 mg of dipotassium oxalate was added immediately after voiding to prevent ammonium decomposition. Using computer program EQUIL 2 the following parameters were calculated: pH of urine, calcium, sodium, potassium, chloride, magnesium, phosphate, sulfate, ammonium, urate, oxalate, citrate, cystine and creatinine (mmol/L) using values of urinary volume from 24-hour. The 24-h urinary excretion was calculated and expressed as a ratio to creatinine for each of the measured urinary components. Using J4.8 machine learning Algorithm in a form of decision tree (Weka implementation of landmark C4.5 Revision 8) further interaction of calcium, oxalate and citrate was calculated [14,15].

3. Results

Repeated ultrasound examination revealed no anomaly of the urinary tract. We excluded hypercalciuria, hyperoxaluria hypocitraturia, hyperuricosuria, renal tubular acidosis, cystinuria, aminoaciduria and depletion of glycosaminoglycans (Table 1).

Urine saturation with either calcium oxalate or brushite was normal. Urine culture taken after ceftriaxone treatment implementation was repeatedly sterile. Infrared spectroscopy of passed urinary stone showed a mixture of calcium hydroxy carbonate phosphate and ceftriaxone. An increased calcium excretion was found during ceftriaxone treatment in comparison with the follow-up at 2 months, albeit not in the range of hypercalciuria. The fourth step of J 4.8 Classifier Alghorithm decision tree has clasified this patient as a potential calcium oxalate stone former. Within 6 months after discontinuation of ceftriaxone therapy an abdominal ultrasound revealed spontaneous resolution of both urine and gallbladder stones in this boy.

Table 1. Urinary calcium excretion during treatment and promoter/inhibitor individual parameters, ratios and urine saturation 2 months after medication

		Normal values (age and sex related)
Calcium excretion during medication		
Calcium/creatinine mmol/mmol	min. md. max. 0.36 0.43 0.48	0.56
Calcium excretion (mg/kg/24h) min md max	min md. max. 2.33 2.92 3.51	4
Urine promoter/inhibitor parameters 2 mo after medication		
Urine pH profile = 5-6		
Calcium/creatinine (mmol/mmol)	min. md. max. 0.08 0.19 0.41	
Calcium excretion (mg/kg/24hr)	min. md max. 0.70 1.61 3.03	
Oxalate/creatinine (mmol/mol)	44.30	76
Citrate/creatinine (mmol/mol)	185.00	736
Urate/creatinine (mmol/mmol)	0.39	1.03
Cystine (μmol/24hr)	43.00	316
Sodium/creatinine (mmol/mmol)	3.11	25.4 *
Phosphate/creatinine (mmol/mmol)	2.05	2.44*
Magnesium/creatinine (mmol/mmol)	0.32	1.01*
Sulfate/creatinine (mol/mol)	1.65	4.97
Chloride/creatinine (mmol/mmol)	15.30	22.6 *
Ammonium/creatinine (mmol/mmol)	0.42	6.11*
Glycosaminoglycans/creatinine (mg/g)	2.96	15
Citrate/calcium ratio (mmol/mmol)	0.94	3.59 *
Magnesium/calcium x oxalate ratio (mmol)	1.06	3.31 *
Oxalate/citrate x glycosaminglycans ratio	2.87	34.8 *
Urine saturation (calcium oxalate)	2.575	8.4
Urine saturation (brushite)	8.602	13

Md, median; min, minimum; max, maximum
**max.values, healthy Croatian children [10,11]*

4. Discussion

Ceftriaxone can be found crystallized with free ion calcium to form aggregates in dose-and time-depending manner [16]. As both ceftriaxone and carbonate phosphate

possess high calcium-binding affinity, such mixture has high potential for a stone formation, especially when the calcium urinary excretion is increased [10,16]. A recent study has proven a convincing association of increased calcium excretion with ceftriaxone treatment [9]. Such formed stones are fairly rarewide use of ceftriaxone, yet additional risk(s) factors for stone formation are still expected. Therefore, we tried to evaluate possible disturbance(s) of promoter/inhibitor factor(s) and to link them with the promotion of ceftriaxone crystallization [16]. However, failed to demonstrate any predisposition or elevated risk of stone disease based on biochemical analyses, including urine glycosaminogycans and urine saturation. Urine glycosaminoglycans were examined previously in urinary calcium phosphate stones [17]. is the first case report of urine glycosaminoglycans and urine saturation in patient with cephtriaxone urinary stones. We observed an increased level of calcium excretion during ceftriaxone treatment as compared with the same analysis performed 2 months later, which is in accordance with previous observations [9]. However, urinary calcium excretion was not in the range of hypercalciuria. We assume that considerable calcium consumption has occured during lithiasis formation, leaving less calcium for excretion in the urine. Nevertheless, it proves the importance of calcium homeostasis in urine with ceftriaxone and an increased risk of urinary stone disease in general. J4.5 Classifier decision tree on fourth step has classified our patient as having a weak risk for calcium oxalate stone disease. This was somewhat unexpected as the stone consisted of ceftriaxone and calcium hydroxy carbonate phosphate, but not of calcium oxalate. In our opinion ceftriaxone medication may serve as a trigger for acceleration of stone formation in the urine that is already verging on unbalance of many potentially lithogenic compounds. Concomitant urinary tract infection may also favour this event. However, such infections should favour phosphate lithiasis, so that a weak potential for the formation of calcium oxalate stone can be overcome. Ceftriaxone has probably increased urine supersaturation to a critical limit and in addition to urine phosphate excretion it has boosted product solubility to an extent which caused a large-scale spontaneous precipitation of crystals [18]. A possible prevention of such stone formation would be to maintain alkaline urinary pH during ceftriaxone therapy and look out for concomitant urinary tract infection with nanobacteria [18]. Our data is pointing out that a search for causes of ceftriaxone urolythiasis is less plausible in the urine following, rather than in the stone formation phase [9]. Although, we suppose that urineanalysis during acute stone formation phase will provide more consistant results.course, a single case report bears significant limitation to this conclusion. Further, limitation to metabolic evaluation is a lack of supersaturation references in children [19,20]. Spontaneous resolution of calcium hydroxy carbonate phosphate/ceftriaxone counters against the mixture's firm stability. Similar spontaneous stone resolution in the biliary tract seems to support such hypothesis [21]. Since stone reverseability has occured in our boy patient we considered calcium phosphate-calculated saturation of brushite, and not apatite, fairly adequate for such instable solution [22,23].

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