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Chronic urine acidification by fludrocortisone to treat infectious kidney stones

Acidification chronique de l'urine par la fludrocortisone afin de traiter les calculs rénaux infectieux

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Abstract. Chronic urinary tract infections by urease-producing bacteria may increase urine pH and promote thereby the formation of recurrent kidney stones made of highly carbonated calcium phosphate apatite and struvite, a magnesium ammonium phosphate. To date, there is no safe and effective treatment decreasing urine pH on a long term. We hypothesized that fludrocortisone, a mineralocorticoid, would decrease urine pH by increasing proton secretion in the kidney collecting tubule. We report three cases of patients with kidney stone suffering from chronic urinary infection by urease-producing germs, treated by fludrocortisone on a long term. Urine pH decreased sustainably over several months and tolerance was good.

Résumé. La lithiase urinaire infectieuse survient chez les patients dont le pH urinaire est alcalin, suite à l'activité uréasique de bactéries colonisant leur urine. Il n'existe pas à l'heure actuelle de traitement sûr et efficace permettant d'acidifier l'urine. Nous avons émis l'hypothèse que la fludrocortisone, un minéralocorticoïde utilisé en pratique clinique, augmente la sécrétion tubulaire de protons dans le tube collecteur et pourrait acidifier l'urine efficacement. Nous rapportons ici trois cas de patients atteints de maladie lithiasique infectieuse particulièrement récidivante et traités par fludrocortisone au long cours, chez qui le pH urinaire a diminué de façon importante durant plusieurs mois.

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Keywords. Kidney stone, Infection, Urine pH, Fludrocortisone, Crystallization.
Mots-clés. Lithiase urinaire, Infection, pH urinaire, Fludrocortisone, Cristallisation.
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1. Introduction

Infectious urolithiasis accounts for 10 to 15% of all urinary stones [1]. The development of infection-related urinary stones is promoted by alkaline urine. Actually, chronic urinary tract infection by urease-producing bacteria increases pHu. The bacterial urease hydrolyses urea to produce ammonia and carbamate, then carbamate rapidly hydrolysis to ammonia and carbonic acid. Urease activity increases thereby pHu, frequently above 7.0, promoting calcium phosphate supersaturation (apatite, pKa 6.8) and its crystallization in urine. Calcium phosphate stones promoted by urea-splitting bacteria frequently contain high amounts of carbonate due to increased bicarbonate concentration in urine [2]. Calcium phosphate phases are mainly carbonated apatite (CA) and amorphous carbonated calcium phosphate (ACCP). Magnesium ammonium phosphate (struvite) is also frequently identified in infectious stones. The presence of struvite even in small amounts in urinary stones is pathognomonic for the presence of urease-producing bacteria. The crystallization of struvite is promoted by both increase in pHu (pKa 7.2) and increase in ammonia production; the role of magnesium in its formation remains poorly understood [3, 4]. Finally, infectious stones may contain ammonium urate (AmUr), usually as a minor component, whose crystallization is promoted by alkaline pH (pKa 7.95) and high concentration of ammonia (and urate) [5,6].

Urine culture from patients with infectious stone may be negative or reveal the presence of other bacteria without urease activity, suggesting that low-grade urease-producing bacteria are present in the kidney stone vicinity but may not be always successfully identified [7–9]. Both gram-positive and gram-negative species can have urease activity. The most frequently incriminated bacteria with urease activity are *Proteus mirabilis*, *Staphylococcus*, *Pseudomonas*, *Providencia* and *Klebsiella*.

Because the supersaturation of struvite, AmUr and CA is increased by alkaline pH, acidification of urine can be helpful in the management of infectious stone [10]. Moreover, urine alkalinization may be promoted by a lack of proton supply in the distal part of the renal tubule (distal tubular acidosis), by chronic digestive loss of hydrochloric acid (vomiting or gastric aspiration) or by ion exchange (chloride and bicarbonate) in patients affected by urinary diversion with intestinal segments. The latter case is at risk for chronic colonization by urea-splitting germs.

Direct delivery of acid valences through ammonium (sulfate, nitrite or chloride) or oral L-methionine (metabolized to sulfate and hydrogen ions) has been tested to acidify urine of patients suffering from infectious urolithiasis [11]. However, this strategy induces gastrointestinal tract irritation and systemic hyperchloremic acidosis with headaches and dizziness.

Therefore, we suggest a new way to sustainably acidify urine by increasing tubular proton secretion in the collecting duct. For this purpose, we were inspired by the acute urine acidification tests described by Walsh *et al.* [12]. Indeed, this study demonstrated capacity of the distal part of the nephron to acidify urine after a single administration of 1200 μg fludrocortisone, a mineral corticoid. The acidification capacities of the kidney were considered as preserved if pHu decreased lower than 5.3 after a single dose. Fludrocortisone induces principal cell sodium reabsorption and alpha-intercalated cells H^+ secretion in the distal nephron [13]. However, this high dose of fludrocortisone is not acceptable for a daily use. We hypothesized that fludrocortisone on a long term and at a milder dose (100 μg BID) would reduce pHu and could thereby prevent infectious stone formation (Figure 1). We present herein the preliminary results obtained in three patients treated on a long term with fludrocortisone for urinary infectious stone.

2. Patients and methods

We report three cases of patients referred to our nephrology unit for urolithiasis. All patients were affected by infectious urolithiasis and had high pHu.

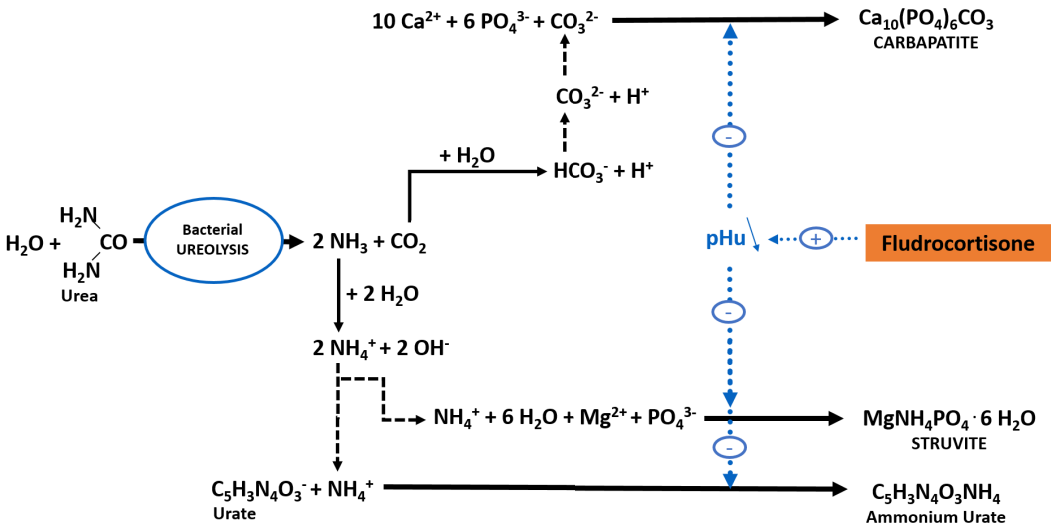

Figure 1. Concept of the use of fludrocortisone for slowing down the process of infectious urolithiasis. Blue dotted arrow: representation of the effect (positive or negative) of fludrocortisone on pHu and of pHu on the formation of carbapatite, struvite and ammonium urate; black arrow: chemical reaction; black dotted arrow: origin of the molecules (i.e. it is not the exact chemical reaction).

None of them had conditions that would have contraindicated the use of fludrocortisone, i.e. hypersensitivity to fludrocortisone, cirrhosis, hypertension and heart failure, thyroid disease, myasthenia or ocular infection due to herpes simplex virus. After receiving information relative to potential side effects, they all gave informed consent for testing the mineralocorticoid treatment on a long term, to acidify their urine. Fludrocortisone (Flucortac®) was started at 50 µg BID, with monitoring of serum potassium level and pHu. If the pHu did not fall below 7, the dosage of fludrocortisone was increased to 100 µg BID with a new control of serum potassium level. Clinical tolerance was assessed in parallel.

3. Results

3.1. *Patient no. 1*

Patient 1 was a 28-year-old man with spinal muscular atrophy type 1. He was bedridden, diabetic, with gastrostomy feeding, indwelling urinary catheter and mechanical ventilation by tracheostomy. Enteral nutrition provided 1.397 kcal and hydration was 1.5 l/24 h. His body mass index (BMI) was 18. The first stone episode occurred when he was 7 years old. He experienced five extracorporeal shock-wave lithotripsies and was hospitalized several times for urinary tract infections and sepsis. At the age of 26, stone formation accelerated with the need for four ureteroscopy (URS) treatments, and two admissions in intensive care unit in 24 months. The spectromorphometric analysis concluded in ammonium urate stones of subtype IIId, composed of 90% ammonium urate, 5% CA and 5% struvite. Biological assessment (Table 1) revealed a serum creatinine at 0.9 mg/l (7.9 µmol/l), a 24 h urine volume at 1.4 l containing urea 13 g (216 mmol)/24 h, uric acid 363 mg (2.15 mmol)/24 h, Na^+ 45 mmol/24 h, K^+ 38 mmol/24 h, Cl^- 41 mmol/24 h, Ca^{2+} 13 mg (0.32 mmol)/24 h and oxalate 15 mg (166 µmol)/24 h. Urine pH was 8.0. The cytobacteriological examinations of the urine (CBEU) revealed the presence of three different urease-producing bacteria: *Pseudomonas aeruginosa*, *Serratia marcescens* and *Proteus mirabilis*. Flucortac® treatment was started at 50 µg BID and increased to 100 µg BID. Urine pH decreased from 8 to 5 (month 1), 7 (month 2) and 6 (month 3, Figure 2). A CT-scan performed 3 months after initiation of fludrocortisone showed stable kidney stones and the presence of a bladder stone at the end of the ureteral catheter. The stones were removed by flexible ureteroscopy. The

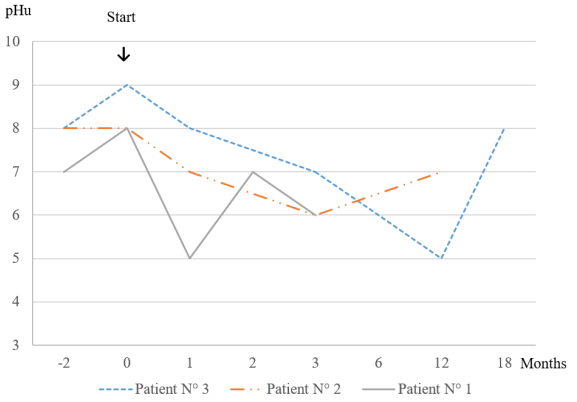

Figure 2. pHu before and after treatment by fludrocortisone.

stones were CA subtype IVa, consisting of 90% CA, 5% ammonium urate and 5% struvite. Under treatment, the patient presented mild lumbar oedema without hypertension. He experienced an episode of hypokalaemia rapidly corrected by potassium oral supplementation.

3.2. *Patient no. 2*

Patient 2 was a 40-year-old woman patient with spina bifida. A lumbosacral myelomeningocele-induced hydrocephalus was treated with a ventricular peritoneal shunt. She was affected by paraplegia, osteoporosis and neurogenic bladder symptoms. A trans-ileal ureterostomy (Bricker's diversion) was performed in 2013. After the Bricker's diversion, she had episodes of hyperkalaemia and a mild hyperchloremic acidosis (chloride 113 meq/l, CO_2 20 meq/l), attributed to ion exchanges between the urine and blood through the digestive mucosa. She received sodium polystyrene sulfonate to decrease serum potassium levels. Two large stones were incidentally identified in the right kidney in 2016, measuring 25 × 13 mm and 20 × 16 mm and with a low density on CT-scan (530 Hounsfield Units). The patient underwent two flexible ureteroscopies during the next two years, due to the recurrence of kidney stones in the right kidney. Unfortunately, none of the stones were analysed. After an increase in drinking water, the urine tests showed: pHu 8, diuresis 2.2 l/24 h, urea 10.3 g (171 mmol)/24 h, Ca^2 + 213 mg (5.31 mmol)/24 h, phosphorus 44 mg (0.64 mmol)/24 h, uric acid 275 mg (1.63 mmol)/24 h and oxalate 17 mg (188 µmol)/24 h. CBEU identified two urea-splitting bacteria, *Klebsiella pneumoniae* and *Proteus mirabilis*. Flucortac® was started at 50 µg BID then increased to 100 µg BID. Urine pH decreased from 8 to 7 (month 1), 6 (month 3), 7 (month 6) and 7 (month 12). Concomitantly, serum potassium levels decreased and sodium polystyrene sulfonate was discontinued. The patient developed slight oedema of the lower limbs without arterial hypertension.

3.3. *Patient no. 3*

Patient 3 was a 26-year-old woman with spina bifida. Myelomeningocele was also responsible for hydrocephalus, paraplegia and neurological bladder. A trans-ileal ureterostomy was performed in 2017. Two renal stones appeared one year after the surgery. They were removed with flexible ureteroscopy but not analysed. The disease recurred, with three new kidney stones over two years. Urine analysis found: diuresis 1.7 l/24 h, pHu 8 and 9, Na^+ 85 mEq/24 h, uric acid 462 mg (2.74 mmol)/24 h, Ca^{2+} 87 mg (2.17 mmol)/24 h, phosphorus 377 mg (12.16 mmol)/24 h, urea 15 g (245 mmol)/24 h, oxalate <2 mg/24 h (<22 µmol). CBEU was positive for *Escherichia coli* but no urease-producing bacteria could be evidenced. Flucortac® was started at 50 µg BID. Under treatment, the urine pH dropped: 9 (month 0), 8 (month 1), 7 (month 3), 6 (month 5). At 1 year the urine pH was 5. At that time, the patient was under antibiotic treatment for an infection of the vertebral osteosynthesis pin. The patient described spontaneous expulsion of stones through the ileal stoma. CT-scan at 12 months showed a single 6 mm stone in the left kidney. Eighteen months after initiation of the treatment the urine pH was back to 8. The patient did not develop oedemas, hypertension or hypokalaemia.

4. Discussion

We report the use of mineralocorticoids in three patients in order to acidify their urine. All three presented typical characteristics of patients with infectious stone: reduced mobility, presence of bacteria with urease activity responsible for increased pHu, multiple urological interventions and in two out of three cases a urinary intestinal diversion. Patients'

Table 1. Biological values before and after fludrocortisone

	Patient no. 1		Patient no. 2		Patient no. 3	
Delay after fludrocortisone (months)	0	3	0	4	0	8
Serum						
Creatinine mg/L (μmol/L)	0.9 (7.9)	0.9 (7.9)	4.1 (36.2)	4.2 (37.1)	5.2 (45.9)	8 (70.7)
Potassium (mEq/L)	3.9	3.5	5.7	3.7	4	4.8
Bicarbonate (mmol/L)	21	22	20	31	28	31
Urine						
24 h Volume (L)	1.4	2	2.2	2.4	1.7	1.5
BUN g/24 h (mmol)	13 (216)	10 (166)	10.3 (171)	10.6 (176)	15 (245)	16.4 (275)
Creatinine mg/24 h (μmol/24 h)	54 (477)	20 (176)	440 (3890)	380 (3360)	510 (4508)	626 (5533)
Calcium mg/L (mmol/L)	9 (0.22)	38 (0.94)	97 (2.42)	34 (0.84)	51 (1.27)	26 (0.64)
Calcium mg/24 h (mmol/24 h)	13 (0.32)	76 (1.89)	213 (5.31)	94 (2.34)	87 (2.17)	39 (0.97)
Phosphorus mg/L (mmol/L)	—	182 (5.8)	20 (0.64)	140 (4.51)	222 (7.16)	522 (16.8)
Phosphorus mg/24 h (mmol/24 h)	—	364 (11.74)	44 (1.4)	336 (10.8)	377 (12.16)	783 (25.25)
Uric acid mg/L (mmol/L)	250 (1.48)	—	125 (0.74)	140 (0.83)	272 (1.61)	324 (1.92)
Uric acid mg/24 h (mmol/24 h)	363 (2.15)	—	275 (1.63)	336 (1.99)	462 (2.74)	486 (2.89)
Oxalate mg/24 h (μmol/24 h)	15 (166)	—	17 (188)	22 (244)	<2 (22)	<2 (22)
Oxalate mg/L (μmol/L)	10.7 (188)		7.7 (85.5)	9.1 (101.6)	<2 (22)	<2 (22)
pHu	7	6	8	6	8	5
CBEU	*P. aeruginosa* *S. marcescens* *P. mirabilis*	—	*K. pneumoniae*	*E. coli* and *P. aeruginosa*	*E. coli*	*E. coli*

pHu were between 7 and 9 before treatment and decreased in all cases with fludrocortisone. We thus observed efficient urine acidification for these patients while the dose of mineralocorticoid used was six times less than proposed by Walsh *et al.* for the acute functional acidification test [12]. Some preliminary studies allowed us to hope for these results. Aperia *et al.* studied the urine acidifying power of mineralosteroids in 1974 [14]. The test consisted of an ammonium chloride load and a bicarbonate infusion, before and after 4 to 6 days of mineralocorticoid treatment in five young girls. The children received 400 μg/1.73 m^2 body surface/day of fluorohydrocortisone with a supplement of potassium. In all patients the urine acidification occurred during fluorohydrocortisone administration.

There is probably an attenuation of the urine acidification effect over time, as shown by the pHu of patients 2 and 3, which was above 7 after one year of treatment. This loss of efficacy over time could be due to the adaptation of bacteria with the induction of urease enzyme activity and/or to the loss of urine acidification capacity by the distal nephron. Even if urine acidification might not persist through time, the use of fludrocortisone may be of help to slow down infectious urolithiasis formation. Although this benefit cannot be stated with certainty in our patients, patient no. 1 modified his urolithiasis profile. Indeed, kidney stone components changed from 90% AmUr (pKa 7.95) to 95% CA (pKa 6.8). This change in crystalline nature could reflect the decrease in pHu. For patients no. 2 and no. 3 we can only note the absence of new stone formation without being able to affirm that this is due to fludrocortisone.

pHu is directly influenced by the presence of bacteria. But variations in pHu can also influence the bacteria behaviour in the urinary tract. Urine acidification could reduce bacterial growth and decrease its cytoadherence [15,16]. It could also have a synergistic effect with antibiotics since the activity of many antibiotics becomes optimal with acid pH [17,18]. However, antibacterial effects of acid pH have been demonstrated only *in vitro*. In a polymicrobial environment it cannot be excluded that acidification

leads to the emergence of a subgroup of acidophilic bacteria. It remains to be determined whether fludrocortisone allows a significant decrease in urine pH to obtain an antibacterial effect.

Treatment with fludrocortisone needs to be done with caution, as patients may be affected by short-term and long-term side effects, particularly electrolyte imbalance. There is a risk of sodium retention contraindicating its use in patients affected by uncontrolled hypertension, cirrhosis and heart failure. Fludrocortisone-induced fluid retention resulted in oedema in two of our patients. Oedema was limited and the use of diuretics was not necessary. If the situation had required it, we would have had the choice of either discontinuing fludrocortisone administration or adding a diuretic. In this case, the use of a loop diuretic would increase the flow of sodium to the distal nephron and, in theory, maintain (or even increase) the acidifying power of the urine by fludrocortisone. The second early adverse effect observed was hypokalaemia in patient no. 1. Metabolic alkalosis and hypokalaemia are due to the urinary excretion of H^+ and potassium, respectively, under the action of fludrocortisone. Hypokalaemia is easily detected by blood tests and can be corrected by oral potassium supplementation. These biological modifications can sometimes be beneficial for the patients. This was the case for patient no. 2 who had a trans-ileal urine diversion. In this type of surgery, the contact of the urine with the digestive mucosa is responsible for chloride/bicarbonate ion exchanges which lead to hyperchloremic metabolic acidosis and hyperkalaemia. In this case, fludrocortisone can help to correct the metabolic acidosis and thus control hyperkalaemia. Long-term use of fludrocortisone could expose patients to hepatic glycogen accumulation that could adversely affect nitrogen balance if protein intake is inadequate [19,20]. Fludrocortisone may also increase bone turnover inducing osteoporosis with increased urinary calcium excretion [19,21]. However, urine calcium excretion was relatively low in the three patients. The main risk with a long-term use of fludrocortisone remains adrenal insufficiency. It results from a progressive inhibition of corticotrophin secretion by fludrocortisone. This inhibition occurs at prolonged and high doses (400 μg/day) of fludrocortisone [22]. Moreover, patients with infectious urinary lithiasis present high risk for urinary tract sepsis with acute exacerbation of underlying adrenal insufficiency. Therefore, fludrocortisone dose should be less than 400 μg/day and/or prescribed for a limited period of time. Patients and caregivers should be informed and educated about the risk of adrenal insufficiency in the event of sepsis on fludrocortisone. In this way, bacterial infections can be treated quickly and adrenal insufficiency detected early. Risk of malnutrition should also be prevented, and osteoporosis should be detected and treated in case of treatment duration over one year.

Infectious stones are a serious cause of morbidity and mortality for which treatment is still unsatisfactory. These fast-growing stones may reappear quickly, within 4 to 6 weeks following surgery [23,24]. Complete removal of stones by surgery is essential: patients with struvite stone fragments three months after a surgery have a higher rate of stone progression (+78%) than stone-free patients [25]. Antibiotics have a pertinent role pre-operatively, post-operatively and potentially in the presence of residual stone fragments. However, evidence for specific antibiotic regimens is lacking and guidelines are not prescriptive regarding the nature of the molecules to be used, their dose and duration of treatment [26–29]. Other treatment strategies have failed. The urease inhibitor (acetohydroxamic acid) has only shown a modest benefit with many side effects (22 to 62%) and is no longer used [30–32]. Citrate forms protective complexes with Ca^{2+} and Mg^{2+}, limiting in theory stone formation, but is lost in infectious conditions due to the metabolism of citrate by bacteria [18]. Thus, after supporting surgery with antibiotics, secondary prevention of infectious stones is often disappointing and limited to increased water intake and correction of potential nutritional risk factors. New therapeutics are therefore required and we think that the use of fludrocortisone in order to acidify urine deserves further investigation. Its use in a selected population seems to be safe but the modality of use must be specified and its effectiveness monitored. Fludrocortisone could be particularly useful for patients with digestive urine diversion to prevent or treat hyperchloremic acidosis and hyperkalaemia. This treatment could also be used as secondary prevention after surgery of infectious stones.

Our study suffers from limitations. The most important is the lack of a control group. In the absence of a control group, we cannot state that the changes in pHu that we observed in our patients are totally at-

tributable to fludrocortisone. Although the pHu decreased in the three cases, the limited number of patients did not allow to draw any definitive conclusion and we could not perform relevant statistical analyses. Moreover, pHu may vary during the day. These variations depend on the pharmacokinetics of Flucortac® but also on food intake. Further studies may focus on pHu variations over the diurnal cycle under treatment. Finally, as evidenced by patient no. 3, urine acidification can be influenced by the use of antibiotics if they are effective on the urease-producing bacteria present in the urinary tract. Nevertheless, pHu dropped early and sustainably in patient no. 3, before the onset of antibiotics.

5. Conclusion

Fludrocortisone appears to be a potential therapeutic tool in the treatment of infectious urolithiasis. It may actually decrease pHu by increasing proton secretion by the distal nephron. The expected benefit of this treatment is to increase the solubility of struvite, AmUr and CA with also potential antibacterial effects. Moreover, fludrocortisone use could decrease the risk of hyperchloremic acidosis induced by digestive urine diversions. We reported three cases with decreased pHu after fludrocortisone use and good tolerance. Further studies are needed to determine the best strategy for the use of this therapy (patient typology, dosage, presence of concomitant antibiotics use, duration) and to confirm clinical benefits for the patients.

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