Struviren®

1. Introduction to phosphate stones

1.1. Supersaturation

Urine supersaturation with insoluble salts of calcium oxalate or calcium phosphate is the driving force for stone formation[1]. Calcium phosphate supersaturation increases rapidly as urine pH rises above 6,2[1].

1.2. Calcium phosphate stones

1.2.1. Chemistry of calcium phosphate in urine

The formation of phosphate salts depends on the dissociation of phosphoric acid (H3PO4) in urine. In the physiological range of urine pH, dihydrogen phosphate ($H_2PO_4^-$) and monohydrogen phosphate (HPO_4^{-2}) ions coexist at approximately equal concentrations[2].

Calcium phosphate is present in urine mainly as dihydrogen calcium phosphate Ca(H2PO4)2, monohydrogen calcium phosphate ($CaHPO_4$, known as brushite) and calcium phosphate ($Ca_3(PO_4)_2$) (in the form of hydroxyapatite and carbonate apatite salts). Conversion of Ca(H2PO4)2 to brushite and brushite to apatite depends on urine pH[2].

Brushite ($CaHPO_4$) is very insoluble in urine, whereas dihydrogen calcium phosphate (Ca[H2PO4]2) is soluble. In urine pH 4,5-6,8, Ca(H2PO4)2 has good solubility and no tendency to form crystals. As urine pH rises to more alkaline values, Ca(H2PO4)2 gives up a proton and transforms to brushite that is insoluble and tends to precipitate[3].

The pKa of Ca(H2PO4)2 is 6.8, so at pH 6.8 is already 50% converted to $CaHPO_4$ (brushite). As urine pH increases to values higher than 6.8 a greater than 50% conversion of soluble Ca(H2PO4)2 to insoluble $CaHPO_4$ (brushite) occurs. On the contrary, as urine pH decreases, solubility of calcium phosphate salts are increasing. At pH values lower than 6.2 the solubility of any calcium phosphate salt is greatly improved[2][4].

In normal urine pH, conversion of brushite to apatite, i.e. crystallization of calcium phosphate [Ca3(PO4)2], does not seem possible[2]. This is due to the fact that subtraction of the last proton of phosphate ion (HPO_4^-) is possible at pH values above 9,5. Nevertheless, transformation to apatite is possible at pH as low as 6,9 in pathological conditions involving urine supersaturation with calcium phosphate[2].

1.2.2. Overview of calcium phosphate stones: apatite and brushite stones

Although the prevalence of calcium phosphate stones is increasing, they still only make up a minority of stone disease[5].

Kidney stones composed predominantly (50% or more) of calcium phosphate constitute up to 10% of all stones and 15%–20% of calcium containing stones. Calcium phosphate is a minor component of up to 30% of calcium oxalate stones as well[3] .

There are several forms of calcium phosphate that appear in kidney stones. The most common form is apatite. Brushite ($CaHPO_4$) is less common, probably because often transforms into apatite. Why some calcium phosphate stones take the form of apatite and others take the form of brushite is not known.

1.2.3. Apatite stones

Infections with urea splitting bacteria favor carbonate apatite formation. Infection is not a prerequisite for the formation of carbonate apatite stones. Apatite can be present in patients with idiopathic calcium phosphate stones not associated with infection[6].

pH values above 6.8 and high calcium concentrations are critical factors that trigger crystallization of apatite. Distal renal tubular acidosis (dRTA) through increased urine pH and hyperparathyroidism through hypercalciuria, hyperphosphaturia and concomitant hypocitraturia may provoke the formation of apatite stones[2].

Lithotripsy is an effective treatment for the disintegration of apatite

Struvite is a phosphate mineral composed of magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4.6H_2O$)[2]. Struvite is formed as a result of urinary tract infection with urease-producing bacteria (e.g. *Proteus* and *Providencia* spp., *Klebsiella pneumoniae*, etc). Urease is an enzyme produced by these bacteria that catalyzes the hydrolysis of urea into carbon dioxide and ammonia. The reaction occurs as follows: $(NH_2)_2CO + H_2O \rightarrow CO_2 + 2NH_3$. Ammonia and carbon dioxide further hydrolyze to ammonium hydroxide and bicarbonate which both cause strong alkalization of urine[2]. The effect of urine citrate, which forms protective complexes with [Ca^{2+}] and [Mg^{2+}], is lost in infective conditions due to the metabolism of citrate by the high concentration of bacteria[2].

1.3.2. Overview of struvite stones

Struvite represents 2-15% of the stones sent for analysis[8]. Stones that contain struvite may originate de novo or grow on pre-existing stones, which are infected with urea-splitting bacteria[8]. There are several factors predisposing patients to struvite stone formation[8].

1.3.3. Struvite stone (or "Infection stone") disease

Struvite stones grow very fast, as conditions are permanently in favor of the formation product[2]. Crystallization has no localized starting point such as a renal papilla or a calyceal niche, but rather occurs simultaneously throughout the whole collecting system[2]. Inflammation leads to increased mucus secretion, and this acts as a matrix for crystal aggregation. Struvite stones under these favorable circumstances, within a few weeks form what is known as "staghorn stones". Staghorn stones most frequently contain not only magnesium ammonium phosphate (struvite) but also apatite. They are branched stones that occupy a large portion of the collecting system. Typically, they fill the renal pelvis and branch into several or all of the calices[2].

Struvite and staghorn stones are commonly referred to as "infection stones" because of their strong association with urinary tract infections. Cultures of "infection stone" fragments obtained from both the surface and inside of the stone have demonstrated that bacteria reside within the stone thereby causing the stone itself to be infected in contrast to stones made of other substances where the stones remain sterile inside[8]. In both struvite and staghorn stones bacteria are always enclosed which contribute to recurrent infections. Over time, untreated struvite or staghorn stones are likely to destroy the kidney and/or cause life-threatening sepsis[8].

1.4. Prophylaxis against recurrence of calcium phosphate, struvite and infection stones

Prophylaxis against recurrence assume particular importance in the management of phosphate stones. In cases of bacteriuria involving urease-producing bacteria, antibiotic treatment is essential[2]. As the solubility of phosphates increases greatly at pH values of less than 6.2, acidification of urine results in dissolution of residual concretions and prevention of new stone formation[2]. Controlled urinary acidification supports the treatment of infection and, at a pH value of less than 6.2 and urine dilution to 2.5Lt/24h, prevents the crystallization of struvite and carbonate apatite[2].

Urinary acidification is contraindicated in all forms of acidosis, especially distal RTA[2]. Furthermore, urinary acidification carries a risk for uric acid crystallization in hyperuricosuria[2].

2. Struviren®

L-Methionine tablets 500mg

2.1. What is Struviren® and what it contains

Struviren® is a "medical food" that contains L-methionine.

2.2. Qualitative and quantitative composition

Each tablet of **Struviren®** contains 500mg of L-methionine as the ingredi

stone-formers on L-methionine therapy were followed over a period of 10 years. Recurrent stone disease was observed in only 10% of cases[10].

In assessments of the efficacy of L-methionine therapy the drop in urinary pH to acidic values was the most relevant factor for metaphylaxis[2]. For infection-induced renal stones, long-term administration of antibiotics in combination with urine acidification by L-methionine (urinary pH 5,8-6,2) is recommended[2]. There was a significant lowering of the rate of bacterial cytoadherence in a study of 33 female patients with chronically recurrent urinary tract infection who were treated with L-methionine[2]. The study established the suitability of L-methionine for the prevention of reinfection in chronic urinary tract infection[2].

2.4. Indicated use

Metabolic acidification of urine as a prophylaxis against recurrence of calcium phosphate, struvite and infection stones or when urine acidification is considered appropriate by the treating physician.

2.5. Dosage and administration

The usual dose of **Struviren®** is one tablet 500mg twice a day. Nevertheless, the daily dosage of **Struviren®** can range between 500 and 3000mg. The most appropriate dosage of **Struviren®** is the dosage that adjusts urine pH between 5,8 and 6,2. The total daily dosage should be divided in two (morning and evening) equal doses. In order to achieve rapid urine acidification, it is useful to start therapy with two tablets twice daily.

2.6. Dose optimization using pH strips

The package of **Struviren®** contains novel pH strips composed of two different pH indicators with a pH range between 4,50 and 9,00. One of the indicators is more sensitive to the lower half (pH 4,50 to 6,50) and the other to the upper half of the pH spectrum (pH 6,75 to 9,00). The most representative assessment of urine pH is carried out with the second urine after awakening. For optimum results, a second pH assessment should be performed within the day, preferably in the evening, before going to bed and on an empty stomach, since food and digestion strongly affect urine pH level. This follow-up assessment intends at providing around the clock adequate control of pH between 5,8 and 6,2. On average, the full effect of methionine on urine pH is manifested after 5-6 days of treatment. The effect of L-methionine in urine pH is evident even after the first dose of **Struviren®**. The patient can therefore adjust urine pH to the optimal range within a few days and define individual dosage schedule.

2.7. Contraindications

Struviren® is contraindicated to patients with: -renal or liver failure -metabolic acidosis -renal tubular acidosis -hyperhomocysteinemia -hyperuricaemia -hyperuricosuria -uric acid stones -cystine stones.

2.8. Precautions

In case of hypothyroidism homocysteine plasma level may increase. Prior to treatment with methionine the thyroid function should be tested.

Co-administration of methionine with the antibiotics ampicillin, sulfonamides or nitrofurantoin may result in prolongation of their plasma half-life and potentiation of their effects, since these weak acids tend to be reabsorbed by urine acidification. There are no adequate studies for the administration of methionine in children. Methionine should therefore not be used in children under 12 years of age.

2.9. Adverse reactions

Blood: In patients at risk of metabolic acidosis shift of blood pH in the acidic range may occur. *Nervous system:* The intake of methionine may cause drowsiness and irritability. *Gastrointestinal tract:* The intake of methionine may cause nausea and vomiting.

2.10. Pregnancy

Category C. **Struviren®** has not been studied in pregnant women in adequate and well-controlled studies. Pregnant women can receive **Struviren®**

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