New Drugs to Prevent Recurrence of Renal Stone Disease

Bo G. Danielson, B. Fellström, M. Lindsjö, S. Ljunghall, and B. Wikström

Summary. Many patients who are stone formers have recurrent stone formation, for which detailed clinical and biochemical work-up is necessary. Even if conventional treatments with thiazides, orthophosphate, or magnesium or potassium citrate are effective in many stone formers, their use may be limited by their way of acting or by their side effects. This is particularly the case in patients with increased urinary oxalate excretion.

Therefore, during recent years, two new approaches have been tried. Since it is known that glycosaminoglycans are potent inhibitors of calcium oxalate crystal growth, aggregation, and possibly also crystal adherence to the walls of the urinary tract, a pentosan polysulfate (PPS), has been tried as a prophylactic treatment in stone formers. Of the patients on PPS treatment 75% were free of recurrences, despite severe stone disease with previous frequent recurrences. Another 10% of the patients experienced considerable reduction in the frequency of the stone episodes.

In patients with enteric hyperoxaluria and severe stone disease, treatment with an organic marine hydrocolloid (OMH)—trade name Ox-absorb—was used to reduce gastrointestinal oxalate absorption. The OMH was shown to bind oxalate in vitro, and to reduce urinary oxalate by oxalate binding in the gut. It was very well tolerated, improved bowel function, showed promising effects on stone episode rate, and had very few side effects.

Introduction

During recent years less interest has been focused on basic mechanisms of stone formation and prophylactic treatment than on extracorporeal shock wave lithotripsy (ESWL) treatment and its consequences.

1Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden
However, there are many patients with severe stone disease, with frequent recurrences where repeated shock-wave treatment is less suitable and where prophylactic medical treatment is more advisable. Even if ESWL may be the easiest way to treat the stone former when he or she presents with a stone, the strategy for long-term treatment has to be considered. Therefore a clinical and metabolic work up of the recurrent stone former is essential.

Renal stone formation is basically a consequence of an imbalance between supersaturation of the urine and the inhibition of crystal formation, growth and aggregation [1]. Urine contains many substances which are claimed to modify the rate of crystallization of calcium oxalate and calcium phosphate. Increased renal excretion of calcium, oxalate, and phosphate contributes to an increased risk of stone formation. The risk can be influenced by the presence of various promoters of nucleation, growth, and aggregation which could contribute to matrix formation and also to epitaxial growth.

However, the urine also contains many substances which inhibit crystal formation through one or two possible mechanisms. Firstly, they may act by complexing either calcium or oxalate ions, thereby reducing the level of calcium oxalate and calcium phosphate supersaturation in the crystallizing solution. Of the urinary inhibitors, citrate and magnesium fall into this group. The other group of inhibitors acts at relatively low concentrations by adsorbing to the surface of the crystals, thereby retarding the rate of crystal growth and agglomeration. Among this group could be mentioned pyrophosphate, heparinoids or glycosaminoglycans (GAGs) like chondroitin sulfate, heparin, heparan sulfate, dermatan sulfate, nephrocalcin, and Tamm-Horsefall mucopolysaccharide. Glycosaminoglycans including chondroitin sulfate, heparin sulfate, keratan sulfate and dermatan sulfate are naturally occurring in human urine. Heparin, however, is not excreted in human urine. It has been shown previously in experimental work that the inhibitor potential of GAGs is dependent on the degree of sulfation and that the inhibitor effect takes place because of reversible binding of the GAGs to the crystal surface, whereby further crystal growth and aggregation become blocked. Experimental studies have also included a pentosan polysulfate (PPS), which has been used for clinical trials in the treatment of urolithiasis.

**In Vitro Study of PPS**

The inhibition of calcium oxalate crystal growth was investigated by seeded crystal procedure, whereby seeded crystals of calcium oxalate were added to metastable calcium oxalate solution together with the inhibitor to be studied. The inhibition of calcium oxalate crystal growth by polyanionic GAGs, Tamm-Horsefall glycoprotein, and pyrophosphate was compared [2]. Using the same system, PPS was also added in order to compare the inhibitory effect. On a concentration basis pyrophosphate was found to be the most inefficient inhibitor tested. Among the polyanions, heparin was the most effective inhibitor, whereas chondroitin sulfate exerted about 40% of the inhibitory activity of heparin. The inhibitory effect of PPS was about 80% of the inhibitory activity found for heparin. The inhibition was directly proportional to the logarithm of the concentration of the polyanions.