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Quantitation of Response to Therapy in Calcium Urolithiasis*

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Summary. The physico-chemical basis for the action of various drugs in calcium nephrolithiasis may be described in terms of changes produced in the urinary state of saturation (APR), limit of metastability (FPR), or in crystal growth. The validation of this scheme for drug action requires further correlation of objective responses to drug therapy, described in terms of urinary crystallisation, with the clinical response.

Key words: Urinary saturation, Metastable solutions, Crystal growth, treatment.

During the past decade, several therapeutic regimens have been recommended for calcium nephrolithiasis. For many of these drugs, a physico-chemical basis of action is beginning to be appreciated.

A brief resume of the physical chemistry of stone formation may facilitate an understanding of the mechanism of drug action. The precipitation-crystallization theory (38, 39), the matrix theory (3, 4, 5), and the inhibitor theory (9, 13, 14) have all been advanced as models for the formation of stones. To date, there is no clear-cut experimental evidence supporting one theory at the exclusion of others. A scheme applicable to all these theories assumes that renal stones form by nucleation of the crystal nidus from a supersaturated solution, followed by growth of the nidus into stone through the processes of crystal growth, epitaxial growth, and crystal aggregation. Requirements for stone formation are therefore supersaturation of urine with respect to stone-forming salts, and increased rates of crystal growth, epitaxial growth or aggregation, as a result of a lack of inhibitors or the presence of promoters. Alternatively, the formation of renal stones may be prevented by measures which decrease the urinary saturation and slow the rates of crystal growth, epitaxial growth or aggregation. The development of techniques (22, 30), for the assessment of the state of saturation, limit of metastability, and crystal growth of urine has allowed us to quantitatively assess the efficacy of the various therapeutic regimes in nephrolithiasis and in some instances to compare these changes with the clinical response to treatment in stone-forming patients. Although the processes of epitaxial growth and crystal aggregation may also be influenced by the various therapeutic regimens, these effects will not be considered because of our lack of personal experience with these methods. Therefore, this discussion will relate the experience of our laboratory in the quantitation of the various therapeutic modalities with respect to nucleation and crystal growth.

TECHNIQUES FOR ASSESSMENT OF "CRYSTALLISATION"

It is generally accepted that urinary activity products of constituent ions of stones potentially provide the best estimates of the urinary state of saturation. Several techniques (8, 22, 30, 35) have been reported for the estimation of activity products of brushite and calcium oxalate. These techniques differ in methodology and have been shown to yield varying results (29). In our approach, the activity products are calculated for the same specimen before and after incubation of urine with synthetic solid phase. In this approach, the solubility of brushite or calcium oxalate monohydrate is determined experimentally in each

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urine specimen. The ratio of activity products (APR) before and after incubation represent the state of saturation, where the ratio of 1 indicates saturation, greater than 1 supersaturation and less than 1 undersaturation. This technique provides a reliable measure of the state of saturation with respect to brushite or calcium oxalate since (a) certain errors inherent in the calculation of the soluble complexes and of ionic strength may be "cancelled" in the APR technique, since they may be present in calculating the activity products in both the initial and final urine, (b) it provides a direct assessment of supersaturation or undersaturation from the extent to which the synthetic solid phase undergoes growth or dissolution in urine as shown by decreases or increases in the concentrations of constituent ions in the ambient fluid.

Urine supports a certain degree of metastably supersaturated state with respect to stone-forming salts. In the metastably supersaturated state, spontaneous nucleation or precipitation of stone-forming salt does not occur even though urine may be supersaturated with respect to that substance. The extent of metastability with respect to stone-forming salts is believed to be dependent on the inhibitors that increase it and on the promoters that reduce it. The limit of metastability indicates the point of nucleation and may be defined by the formation product ratio (FPR) in individual urine samples (30).

Once a crystal nidus has formed, it may grow into a stone of the same composition by the process of crystal growth if the urine is supersaturated with respect to the crystal nidus. Crystal growth in whole urine may be measured by adding to urine a small amount of synthetic solid phase (representing stone) and determining the rate of its growth by measuring the decreases in filtrate concentrations of constituent ions of stone for which growth is being measured (16, 17, 18, 19).

PHYSICOCHEMICAL ACTION OF DRUGS

Techniques of APR, FPR, and crystal growth were utilised to assess the response of stone-formers to treatment with cellulose phosphate, thiazides, orthophosphate, diphosphonate, and magnesium, and to correlate the changes in these parameters with the clinical picture. These actions of drugs are summarised in Table 1.

(a) Sodium Cellulose Phosphate

Sodium cellulose phosphate 1(6, 23, 24, 27) is a nonabsorbable ion-exchange resin with a high affinity for Ca^{2+}. When it is given orally, dietary and secreted calcium exchanges for sodium in the resin and the calcium-cellulose phosphate com plex is excreted in the faeces. It therefore inhibits intestinal calcium absorption by limiting the amount of calcium available for absorption. In this respect, this drug represents the treatment of choice for absorptive hypercalciuria.

In short-term inpatient studies (24) it was observed that sodium cellulose phosphate administered orally to twenty-four patients with nephrolithiasis decreased the urinary APR of brushite even in the presence of a mild-to moderate increase in urinary phosphate. The marked fall in urinary calcium concentration was probably responsible for this decrease in the state of saturation with respect to brushite. On the other hand, sodium cellulose phosphate did not significantly alter the APR of calcium oxalate, or produced a decrease which was less marked than that found for brushite (12, 15). The finding could probably be explained by the stimulation of renal oxalate excretion during therapy. However, in patients undergoing long-term therapy with sodium cellulose phosphate in an ambulatory setting, the change in urinary oxalate is not usually marked.

No consistent change was observed in the FPR or crystal growth of brushite or calcium oxalate, a result which is consistent with the observation that the drug apparently does not modify renal excretion of inhibitors of crystallisation (pyrophosphate, zinc, or citrate) (24).

Long-term studies in sixteen patients with absorptive hypercalciuria (28) who received cellulose phosphate for periods of 1.5 to 4.8 years indicated that the rate of new stone formation was found to decrease during treatment, commensurate with a fall in the urinary state of saturation with respect to brushite. This study represented the first instance in which the clinical response has been correlated with objective changes.

(b) Thiazide

The use of thiazide in the treatment of calcium urolithiasis (41) is based on the ability of the drug to reduce renal calcium excretion. The precise mechanism by which thiazide reduces urinary calcium excretion is not fully understood, but this action makes this drug particularly suitable in the management of patients with renal hypercalciuria (1).

Thiazide therapy invariably reduces urinary calcium and lowers the APR of brushite and calcium oxalate in most partients (25, 40). However, thiazide also increases the renal excretion of phosphate and oxalate, and raises pH in some patients by a mechanism not fully understood. These effects probably overcome the effect of a fall in urinary calcium, and account for the lack of a significant change in the urinary state of saturation with respect to calcium salts encountered in some patients (25, 40).

Table 1. Mode of action of therapeutic modalities

	Na cellulose phosphate	Na phosphate	HCTZ Short-term	HCTZ Long-term	EHDP in vivo	EHDP in vitro
Urinary Ca	↓↓↓	↓	↓	↓↓	-	
Urinary PO_4	↑	↑↑	↑	↑	↑	
Urinary P_2O_7	-	↑↑	↑	↑	-	
Urinary Ox	↑↑	↑/-	↑	↑	↑/-	
Urinary Mg	-	-	↑	-		
Brushite						
APR	↓↓	↑	↓	↓	-	-
FPR	-	↑	↑↑	↑	↑	↑
Crystal growth	-	↓/-	-		↓	↓
Ca oxalate						
APR	-↓	-↓	-↓	↓	-	↑
FPR	-	↑	↑	↑	-	↑
Crystal growth	-	↓/-	-	-	↓	↓

Abbreviations: ↑, increase; ↓, decrease; -, no change; Ox, oxalate; P_2O_7, pyrophosphate; APR, activity product ratio; FPR, formation product ratio; CG, crystal growth.

Another action of thiazide is the promotion of the renal excretion of inhibitors of crystallisation, such as magnesium (25), zinc (34), and pyrophosphate (25). This action of the drug probably accounts for the increase in the urinary FPR of brushite (25) and calcium oxalate (40), observed in some patients. This finding suggests that thiazide therapy may inhibit spontaneous nucleation of these calcium salts. There have been no consistent changes in the crystal growth of calcium oxalate during thiazide therapy (40).

In some patients, hyperuricosuria may develop or become accentuated during thiazide therapy. Because of the recognised interrelationship between hyperuricosuria and calcium nephrolithiasis, careful consideration should be given to the addition of allopurinol to the treatment regimen, particularly if the response to thiazide alone is unsatisfactory.

(c) Orthophosphate

The exact mechanism by which orthophosphate lowers urinary calcium is unknown, but may involve suppression of 1 α,25-$(OH)_2$D synthesis with a resultant decrease in the intestinal absorption of calcium (36).

In short-term studies, orthophosphate therapy increases the urinary APR of brushite (23, 27, 37) owing to the marked increase in urinary phosphate and a comparatively less prominent decrease in urinary calcium. It usually decreased the urinary state of saturation with respect to calcium oxalate (31, 37) because even though urinary oxalate increases slightly in some patients, the decrease in urinary calcium was more prominent. Moreover, orthophosphate promotes renal excretion of pyrophosphate (23, 31, 37) and frequently increases the FPR of brushite (23) and calcium oxalate (31). Effects on crystal growth are variable. Therefore, orthophosphate probably inhibits stone formation by rendering the urine less saturated with respect to calcium oxalate, and by inhibiting nidus formation of brushite and calcium oxalate. Even though urine may become more supersaturated with respect to brushite, the increase in the FPR of brushite apparently compensates for this increase in the state of saturation.

In certain patients, particularly those with urinary tract infection, orthophosphate may fail to augment the renal excretion of pyrophosphate as a result of the action of bacterial pyrophosphatase. In these patients, there is frequently no change in the FPR of calcium salts.

(d) Diphosphonate

Diphosphonate is a synthetic analogue of pyrophosphate which, unlike pyrophosphate, is not hydrolysed in vivo. Therefore, a small fraction of the oral dose is absorbed and after bone has become saturated, appears in urine in an unaltered form. When diphosphonate is added to

urine in vitro, it has been shown to exert inhibition at virtually every step of stone formation. It has been shown to increase the FPRs of brushite (20) and calcium oxalate (11, 33) and to decrease the crystal growth rate for both calcium salts. Diphosphonate probably prevents certain mixed stone formations since it retards the heterogeneous nucleation of calcium oxalate by hydroxyapatite or monosodium urate (26). When diphosphonate is given to patients with calcium urolithiasis, the only consistent effect produced in urine is an inhibition of crystal growth of brushite and calcium oxalate (21). In a long-term study, diphosphonate therapy did not cause consistent increases in the FPR of brushite or calcium oxalate (2).

(e) Magnesium

It has been reported that magnesium is an inhibitor of calcification (18) although not as effective as pyrophosphate. During the administration of magnesium oxide orally (7), urinary pH rises significantly and urinary calcium increases in some patients. These effects probably account for the increase in the urinary APR of brushite. Since urine samples become more supersaturated with respect to brushite, magnesium therapy could promote rather than inhibit stone formation. No significant change in urinary saturation of calcium oxalate is produced. Although a significant increase in the urinary magnesium concentration occurs, no change was found in either the FPR or CG of calcium oxalate or brushite. These results are in agreement with the previous report of the limited inhibitory action of magnesium on the crystal growth of calcium oxalate (18). Therefore, no objective evidence for the beneficial effects of magnesium in calcium nephrolithiasis could be found.

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