8. POTASSIUM CITRATE THERAPY OF NEPHROLITHIASIS

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INTRODUCTION

Potassium citrate is a new and exciting therapeutic modality introduced in 1985 for the management of a wide variety of stone-forming disorders. It has reawakened interest in the deranged citrate metabolism in nephrolithiasis and in the physicochemical effects of citrate in stone formation. It has substantially expanded our capability for an effective medical control of stone disease. The approval of this drug in the United States represented a culmination of our seven years of extensive laboratory and clinical work. This chapter will review this work pertaining to: (1) physicochemical action of citrate, (2) physiological effect of potassium citrate, (3) physicochemical effect of potassium citrate, (4) long-term clinical trial with potassium citrate and safety of potassium citrate.

Rationale for potassium citrate therapy

The U.S. Food and Drug Administration approved the use of potassium citrate in the management of renal tubular acidosis with calcium stones, hypocitraturic calcium oxalate nephrolithiasis ("idiopathic," or secondary to chronic diarrheal syndrome or thiazide therapy), and uric acid lithiasis with or without calcium stones.

The above conditions are characterized by hypocitraturia or unusually low urinary pH. These physiological derangements render the urinary environment prone to crystallization of calcium salts or uric acid, and thus contribute to stone formation. The rationale for the use of potassium citrate is based on
the capability of this treatment to overcome the above physiological disturbances and associated abnormal physicochemical picture. In order to clarify this concept, a brief description of physicochemistry of stone formation and effects of citrate and pH on the crystallization process will be provided.

**Physical chemistry of stone formation** [1]

As described in chapter 2, stone formation begins by formation of the crystal nidus followed by the growth of the nidus into a macroscopic stone by crystal growth, epitaxial growth, and crystal aggregation. Nucleation is the mechanism by which a crystal nidus is formed. It may be homogeneous when crystals form de novo, or heterogeneous when heterologous crystal material is formed. Crystal growth represents growth over the nidus of crystals of the same chemical composition, whereas epitaxy refers to “overgrowth” of heterologous crystalline material. Crystal aggregation describes the process by which preformed crystals aggregate into large clusters.

The following techniques were utilized to quantitate physicochemical effects of potassium citrate. *Relative saturation ratio (RSR)* [2] provides an estimated measure of urinary saturation. The ratio of calculated product of ionic activities in urine (e.g., calcium and oxalate ions) to the thermodynamic solubility product (representing activity product at equilibrium in synthetic medium containing the solid phase) yields relative saturation ratio. *Activity product ratio (APR)* [3], another measure of urinary saturation, is obtained by incubating urine sample to “equilibrium” with a synthetic solid phase against which the state of saturation is being measured. The ratio of activity products before and after incubation represents the state of saturation, where a value of 1 represents saturation, greater than 1 supersaturation, and less than 1 undersaturation.

*Formation product ratio (FPR)* [3] is the lowest supersaturated state at which nucleation is initiated, and therefore defines the metastable limit. Used mainly for well-controlled studies, the FPR is the number of times the urine sample must be supersaturated to allow spontaneous precipitation. *FPR-APR discriminant score (DS)* [4] provides a quantitative measure of the propensity for spontaneous nucleation. The DS reflects both the saturation (APR) and the inhibitor activity (FPR), and thus is a measure of the likelihood for the spontaneous nucleation where positive values represent increased propensity and negative values reduced propensity. *Permissible increment in oxalate (PI)* [5] provides a simpler version for the estimation of the spontaneous nucleation of calcium oxalate than DS. It represents the minimum amount of additional oxalate (as soluble sodium oxalate) that could be added to urine (devoid of crystals) before spontaneous precipitation of calcium oxalate is initiated at 3 hours.

The *concentration of undissociated uric acid* [6] gives a measure of uric acid saturation. It is high at lower urinary pH, particularly below the dissociation constant of 5.5.

Using the above methods, the stone formation as well as prevention may be