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INVITED REVIEW

Jon I. Scheinman · Paul A. Voziyan
John M. Belmont · Sergei V. Chetyrkin · Daniel Kim
Billy G. Hudson

Pyridoxamine lowers oxalate excretion and kidney crystals in experimental hyperoxaluria: a potential therapy for primary hyperoxaluria

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Abstract In order to prevent kidney stones and nephrolithiasis in hyperoxaluria, a new treatment that specifically reduces oxalate production and therefore urinary oxalate excretion would be extremely valuable. Pyridoxamine(PM) could react with the carbonyl intermediates of oxalate biosynthesis, glycolaldehyde and glyoxylate, and prevent their metabolism to oxalate. In PM treated rats, endogenous urinary oxalate levels were consistently lower and became statistically different from controls after 12 days of experiment. In ethylene glycol-induced hyperoxaluria, PM treatment resulted in significantly lower (by ~50%) levels of urinary glycolate and oxalate excretion compared to untreated hyperoxaluric animals, as well as in a significant reduction in calcium oxalate crystal formation in papillary and medullary areas of the kidney. These results, coupled with favorable toxicity profiles of PM in humans, show promise for the therapeutic use of PM in primary hyperoxaluria and other kidney stone diseases.

Keywords Pyridoxamine · Hyperoxaluria · Kidney stones · Nephrolithiasis

J. I. Scheinman (✉) · J. M. Belmont
Department of Pediatrics, University of Kansas Medical Center, 3901 Rainbow Blvd, Room G-019 Miller Bldg, Kansas City KS 66160-7330, USA
E-mail: jscheinman@kumc.edu
Tel.: +1-913-5886031
Fax: +1-913-588-2253

P. A. Voziyan
Departments of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA

S. V. Chetyrkin · D. Kim · B. G. Hudson
Biochemistry, Vanderbilt University Medical Center, Nashville, TN 37232, USA

Introduction

The most common form of kidney stones is calcium oxalate (CaOx), a frequent and increasing condition with a prevalence of 5.2% in the adult population in the US [1]. The recurrence of kidney stones reaches 50–70% in 10 years [2]. While the nidus of most CaOx stones appears to be calcium phosphate (CaP) crystals, the development of stones depends upon urinary oxalate [3]. The level of urinary oxalate is one of the greatest risk factors for kidney stones. Oxalate excretion results from both dietary absorption and endogenous synthesis. There is currently no pharmacological treatment for stone disease that can lower endogenous production resulting in urinary oxalate. There is thus a clear need to develop a new treatment that specifically reduces oxalate production and therefore urinary oxalate excretion. The reduction of oxalate production would most effectively change the chemical equilibrium that predisposes to stone formation.

Primary hyperoxaluria (PH) is the most extreme form of increased endogenous synthesis of oxalate leading to urinary stone formation and nephrocalcinosis with resultant renal failure. PH1 is a genetic defect of peroxisomal alanine glyoxylate aminotransferase (AGT). This defect results in decreased detoxification of glyoxylate to glycine and a consequent increase in conversion of glyoxylate to oxalate (Fig. 1) [4]. PH2 is caused by the deficiency of glycolate reductase/hydroxypyruvate reductase activity 2 in liver cytosol that results in an inhibition of the normal detoxification of glyoxylate through glycolate to L-glycerate.

When we first cared for patients who developed renal failure from PH in 1974 [5], kidney transplantation was contraindicated for PH. From the chemistry of CaOx crystallization, elucidated by Lynwood Smith [6], we developed a strategy that allowed kidney transplantation without recurrence of renal failure [7]. Nevertheless, it requires an intensive strategy for reducing urinary supersaturation (SS) for CaOx, which has been adopted

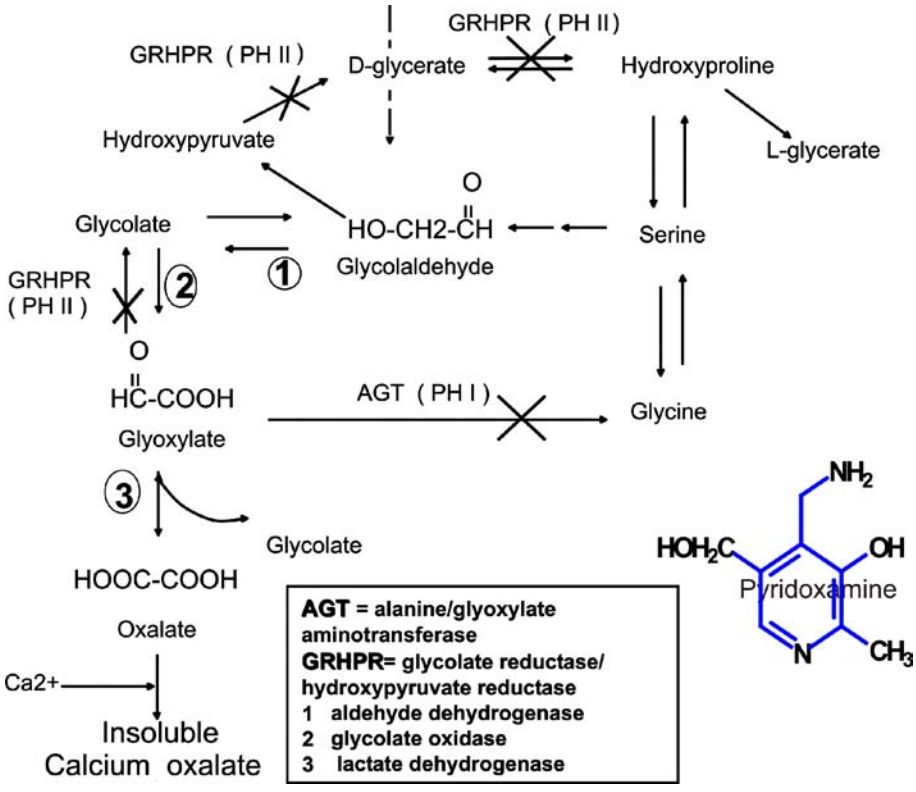

Fig. 1 Major pathways of oxalate biosynthesis in the liver (adapted from Chetyrkin et al. [4]). Sites of metabolic blocks in PH1 and PH2 are indicated by *X*

by every successful transplant program for PH [7, 8]. Failures have been frequent, so that the only currently curative treatment is liver replacement, which carries its own considerable risk. Our studies have shown some continued success of isolated kidney transplantation, and equivalent patient survival by combined kidney/liver transplantation [9]. Lowering urinary oxalate in these patients could alleviate the severity of stone disease and nephrocalcinosis and avoid the need for transplantation, or, after the development of renal failure, might allow more successful isolated renal transplantation. In 2001, we identified 219 patients who had progressed to kidney failure since 1984 before the age of 55 [9]. Thus, PH presents a highly important context for lowering extreme endogenous hyperoxaluria.

Recently, pyridoxamine (PM) has been explored as an agent that can trap carbonyl precursors of oxidative products damaging to basement membranes in diabetes mellitus [10, 11] We proposed that the nucleophilic amino group of PM could react with the carbonyl intermediates of oxalate biosynthesis, glycolaldehyde and glyoxylate, and prevent their metabolism to oxalate. In vitro experiments yielded positive results, and we explored the effects on normal (Fig. 2) and hyperoxaluric (Fig. 3) rats [4].

Methods and materials

Sprague-Dawley male rats (49–52 days old) were housed individually and fed standard powdered stock rations. For more uniform pyridoxamine (PM) administration, the water supply to all animals was limited to 45 ml/day. Animals were randomized on day 3 to receive either ethylene glycol (0.75% w/w in drinking water, EG-group) or no treatment (control). After day 14, animals within each group (control or EG) were pair-matched according to their oxalate level. One member of each pair was then randomly assigned to receive PM (3 mg/ml) either in drinking water (PM-group) or in 0.75% ethylene glycol (EG + PM-group).

The effect of PM on urinary oxalate excretion and kidney crystal formation was studied using this ethylene glycol (EG) rat model of hyperoxaluria. After 2 weeks, PM treatment (180 mg/day/kg body wt) was started and continued for an additional 2 weeks. Urinary creatinine, glycolate, oxalate and calcium were measured. In another 4-week PM treatment experiment, microscopic analysis of kidney tissues for the presence of calcium oxalate crystals was performed.

Results

In control animals, daily oxalate excretion increased during the first 5 days (adaptation period) and then remained relatively stable for the course of the experiment. In PM-treated rats, urinary oxalate levels were consistently lower and became statistically different from controls after 12 days (Fig. 2)

PM treatment resulted in significantly lower (by ~50%) levels of urinary glycolate and oxalate excretion

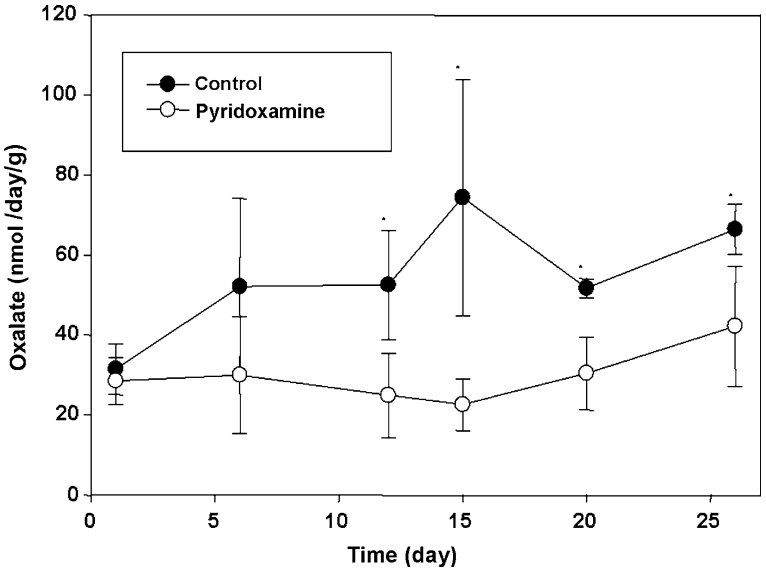

Fig. 2 Effect of PM on oxalate excretion in normal rats

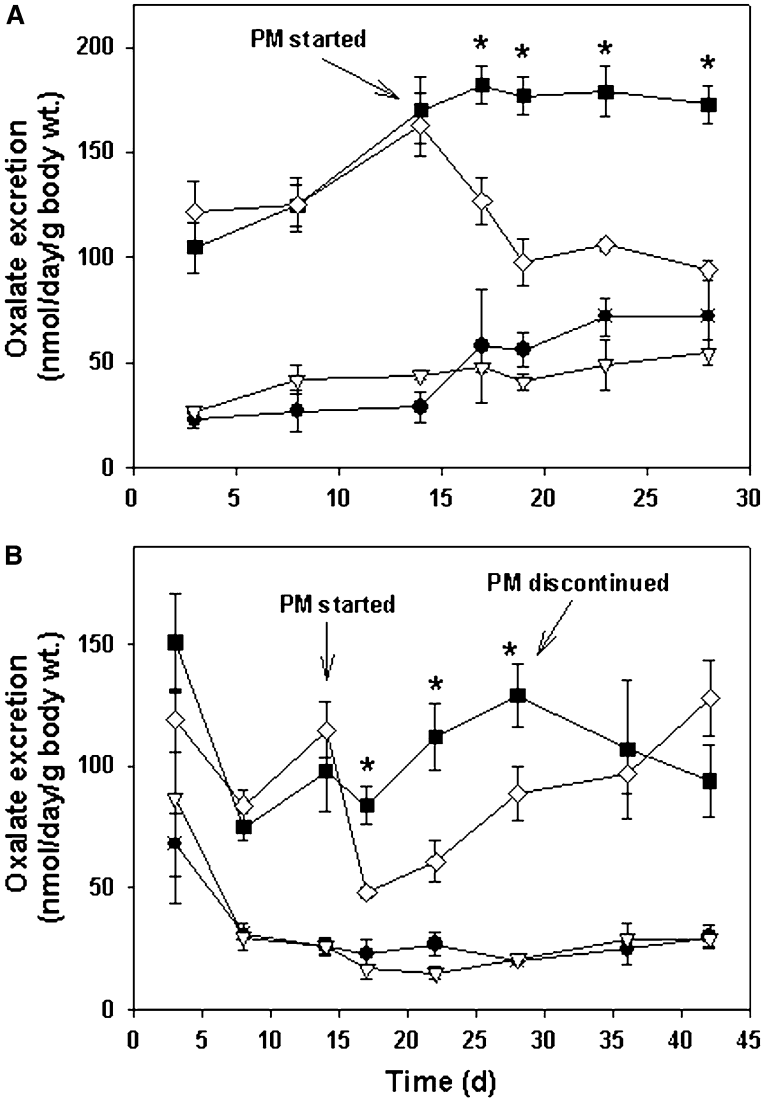

Fig. 3 Effect of PM on oxalate excretion in hyperoxaluric rats. **a** The 28-day experiment used for kidney crystal analysis (Fig. 4), showing a significant decrease in hyperoxaluria by PM. **b** The 42-day experiment showing hyperoxaluria decreased with PM, and returning to hyperoxaluric state after discontinuation of PM

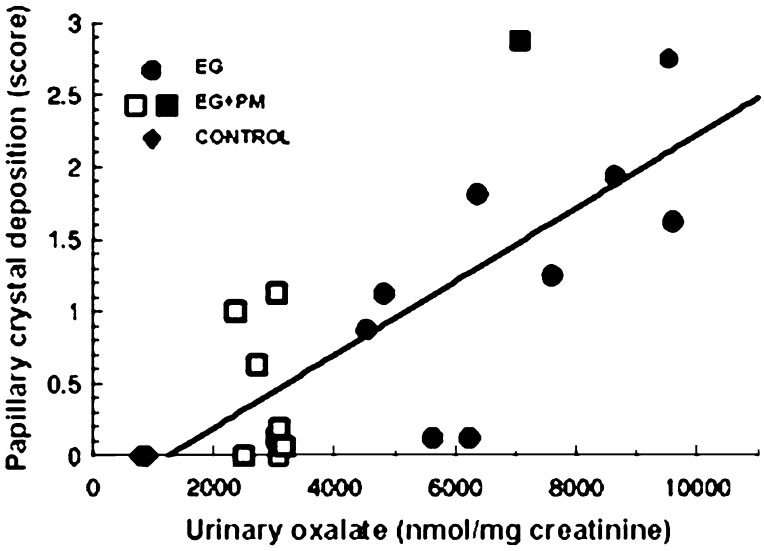

Fig. 4 Papillary/medullary scores of oxalate crystal deposition, related to oxalate excretion. Untreated hyperoxaluric rats (*closed circles*) had greater scores than PM-treated hyperoxalutic animals (*open squares*), with the exception of one rat (*closed square*) which apparently did not respond to PM, by either oxalate excretion or crystal deposition

compared to untreated hyperoxaluric animals) (Fig. 3). This was accompanied by a significant reduction in calcium oxalate crystal formation in papillary and medullary areas of the kidney (Fig. 4), using a reliable scoring system [4].

Pyridoxamine treatment was successful in eight out of nine treated rats (89%). For these animals, the pyridoxamine effect on crystal deposition was statistically significant in both papilla and medulla ($P < 0.02$). In one rat, there was no effect of pyridoxamine on either urinary oxalate or kidney crystal deposition.

Conclusions

These results, coupled with favorable toxicity profiles of PM in humans [10, 11], show promise for the therapeutic use of PM in primary hyperoxaluria and other kidney stone diseases.

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