Urol Res (1994) 22:161–165

ORIGINAL PAPER

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Effect of combined supplementation of magnesium oxide and pyridoxine in calcium-oxalate stone formers

Received: 17 September 1993 / Accepted: 20 December 1993

Abstract A combined supplement of magnesium oxide (300 mg/day) and pyridoxine · HCl (10 mg/day) was given p.o. to 16 recurrent calcium oxalate (CaOx) stone formers, and its therapeutic efficacy was biochemically evaluated by measuring various parameters of blood (Na, K, Mg, urea, creatinine, calcium, phosphate, uric acid, alanine transaminase, aspartate transaminase and alkaline phosphatase) and urine (volume, pH, creatinine, Na, K, Mg, uric acid, calcium, phosphate, oxalate and citrate) at 0, 30, 60, 90 and 120 days of treatment. Serum Mg significantly ($P<0.01$) increased after 30 days of treatment and remained constant thereafter while other blood parameters were unaltered. Combined treatment led to a significant increase in the urinary excretion of Mg and citrate over pretreatment values while oxalate excretion showed a gradual and significant decline during the therapy. The results confirmed the efficacy of MgO-pyridoxine supplementation in terms of changes in urinary excretion of lithogenic and inhibitory components, leading to a significant ($P<0.01$) decrease in CaOx risk index from 0.09 ± 0.04 at 0 day to 0.05 ± 0.02 after 120 days of treatment.

Key words Magnesium oxide · Pyridoxine · Calcium oxalate · Urolithiasis · Therapeutic effect

The recurrence rate of calcium oxalate kidney stone formation is very high with hyperoxaluria as the major predisposing factor for calculogenesis [15, 31]. Vitamin B_6 has been shown to reduce urinary oxalate excretion in primary hyperoxalurics [33] and experimental animals [7]. Administration of pyridoxine · HCl at a dose of 10 mg for 180 days was found to be beneficial in hyperoxaluric stone formers [17]. Stone formation results not only from urinary saturation with stone forming salts but also from lack of urinary inhibitors of crystallization and/or aggregation [23]. Hypomagnesuria is a common finding in stone formers [11, 27], and several investigators have demonstrated beneficial effects of magnesium therapy in prevention of recurrent calcium oxalate and calcium phosphate stone disease [1, 5, 14, 16]. Combined supplementation with magnesium oxide and pyridoxine · HCl is intended to bring about both a reduction in urinary oxalate excretion and an enhancement of urinary magnesium levels, thereby significantly reducing the risk of calculogenesis. Prien and Gershoff [21] have reported a marked decrease in the rate of stone formation, from an average of 1.3 stones per patient per year to 0.10 stones per patient per year during therapy with 300 mg magnesium oxide and 10 mg pyridoxine per day. The biochemical effects on serum and urine parameters responsible for the prevention of renal stones during this therapy have not been studied. Thus, the present study aims to investigate alterations in the serum and urine composition of idiopathic recurrent calcium oxalate stone formers during preventive treatment with magnesium oxide (300 mg/day) and pyridoxine (10 mg/day) for a period of 120 days.

Material and methods

Initially, 32 recurrent calcium oxalate stone formers in the age group of 25–55 years who fulfilled the study criteria were selected for this study from the patients visiting the Urology Department. The inclusion criteria were: (1) minimum of one stone incidence per year during the 3–5 years preceding the therapeutic trial, (2) calcium oxalate as one of the components, revealed by stone analysis of surgically removed or spontaneously passed stone, (3) freedom from urinary infection documented by physical, chemical and pyelographic studies, normal pyelogram and renal function, normal serum

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Table 1 Effect of MgO (300 mg/day) and pyridoxine · HCl (10 mg/day) administration on the serum parameters of stone formers (means ± SD; $n = 16$)

Parameter	Day O	Day 30	Day 60	Day 90	Day 120
Magnesium (mmol/l)	0.82 ± 0.11	0.92 ± 0.07[a]	0.90 ± 0.08[a]	0.94 ± 0.06[a]	0.94 ± 0.05[a]
Sodium (mmol/l)	135.45 ± 5.32	136.8 ± 14.19	134.78 ± 4.68	136.12 ± 5.53	134.93 ± 5.54
Potassium (mmol/l)	4.10 ± 0.44	4.10 ± 0.55	4.12 ± 0.58	4.20 ± 0.54	4.08 ± 0.44
Calcium (mmol/l)	2.39 ± 0.10	2.36 ± 0.16	2.34 ± 0.11	2.35 ± 0.16	2.35 ± 0.17
Phosphorus (mmol/l)	1.12 ± 0.27	1.04 ± 0.13	1.06 ± 0.14	1.08 ± 0.19	1.04 ± 0.11
Creatinine (mmol/l)	0.08 ± 0.02	0.07 ± 0.02	0.08 ± 0.02	0.09 ± 0.02	0.07 ± 0.02
Urea (mmol/l)	4.13 ± 1.27	4.18 ± 1.02	4.38 ± 1.46	4.30 ± 1.18	3.80 ± 0.96
Uric acid (mmol/l)	0.33 ± 0.07	0.34 ± 0.05	0.33 ± 0.05	0.35 ± 0.05	0.33 ± 0.06
Aspartate transaminase (AST; IU)	11.25 ± 3.73	12.75 ± 4.05	11.31 ± 4.52	10.75 ± 3.27	12.31 ± 4.11
Alanine transaminase (ALT; IU)	8.68 ± 3.09	8.87 ± 3.00	9.75 ± 4.05	9.62 ± 2.73	9.56 ± 3.88
Alkaline phosphatase (ALP; KAU)	9.25 ± 2.38	8.68 ± 2.82	9.23 ± 2.43	9.95 ± 2.64	10.00 ± 2.93

[a] $P < 0.01$ for difference from corresponding value on day 0

Table 2 Effect of MgO (300 mg/day) and pyridoxine · HCl (10 mg/day) administration on the urine composition of stone formers (means ± SD; $n = 16$)

Parameter	Day O	Day 30	Day 60	Day 90	Day 120
Volume (l/24 h)	2.50 ± 1.46	2.59 ± 1.49	2.69 ± 1.25	2.69 ± 1.45	2.43 ± 1.63
pH	5.96 ± 0.30	6.07 ± 0.27	6.09 ± 0.26	6.10 ± 0.25	6.12 ± 0.24
Sodium (mmol/24 h)	180.50 ± 53.44	187.25 ± 71.34	181.75 ± 50.70	174.30 ± 58.14	181.75 ± 50.70
Potassium (mmol/24 h)	36.79 ± 19.40	38.48 ± 21.88	35.47 ± 17.18	42.24 ± 16.85	45.36 ± 21.43
Creatinine (mmol/24 h)	9.29 ± 2.42	9.86 ± 2.08	9.99 ± 2.15	10.40 ± 2.51	9.61 ± 2.11
Uric acid (mmol/24 h)	3.13 ± 1.31	2.94 ± 0.84	3.07 ± 0.95	3.46 ± 0.80	2.99 ± 0.79
Calcium (mmol/24 h)	6.43 ± 3.46	6.05 ± 3.12	7.49 ± 3.23	6.62 ± 3.49	8.23 ± 4.50
Phosphorus (mmol/24 h)	25.69 ± 8.17	25.90 ± 6.66	25.64 ± 6.14	26.04 ± 7.37	24.99 ± 8.43
Oxalate (mmol/24 h)	0.68 ± 0.18	0.61 ± 0.17	0.51 ± 0.14[c]	0.43 ± 0.11[c]	0.37 ± 0.08[c]
Citrate (mmol/24 h)	1.52 ± 0.24	1.64 ± 0.28[a]	1.74 ± 0.28[c]	1.91 ± 0.24[c]	2.01 ± 0.22[c]
Magnesium (mmol/24 h)	1.70 ± 0.74	2.08 ± 0.85[b]	2.34 ± 0.80[c]	1.10 ± 0.90[c]	3.21 ± 0.91[c]

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$ for difference from corresponding value on day 0

calcium and phosphorus, absence of any metabolic illness (e.g. peptic ulcer, hyperparathyroidism).

The patients included in the study each received a combined dose of 300 mg/day of magnesium oxide and 10 mg/day of pyridoxine · HCl in capsule form. The patients were advised to avoid high-oxalate foods and any other medication during the study period. During the therapeutic trial 6 patients dropped out at 30 days, another 6 at 60 days and 4 more after 90 days of treatment. Ultimately, 16 patients (10 men and 6 women) with an average age of 37 ± 8 years completed 120 days of treatment.

Clinical follow-up examinations and biochemical assessment of blood and 24-h urine samples (collected on 2 consecutive days) were performed for each patient in the out-patient clinic at 30-day intervals, i.e. upon entry and at 30, 60, 90 and 120 days of therapy. Informed consent was obtained from all the patients taking part in the study.

The volume and pH of 24-h urine samples were recorded and the samples were analysed for creatinine [19], Na, K (flame photometry), Mg (atomic absorption spectrophotometry), uric acid [10], calcium [30], phosphorus [6], oxalate [12] and citrate [32].

The blood samples were analysed for Mg, Na, K, urea, creatinine, calcium, phosphorus, uric acid, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) by routine biochemical procedures [19]. The urinary parameters were expressed as millimoles per decilitre and serum values, as millimoles per litre. A two-tailed Student's paired *t*-test was used to detect the significance of difference, if any in the urine and serum values subsequent to oral administration of MgO and pyridoxine in the group of stone formers in this study.

Results

Table 1 shows the effect of MgO and pyridoxine supplementation on various serum parameters of idiopathic calcium oxalate stone formers. Serum magnesium levels showed a significant increase ($P < 0.01$) after 30 days of treatment compared with the initial levels at day 0, and the levels remained constantly elevated thereafter up to 120 days. All other serum parameters remained unchanged during the 120 days of treatment.

Combined supplementation with MgO and pyridoxine produced a significant ($P < 0.01$) increase in urinary Mg excretion just after 30 days of treatment (Table 2). The urinary Mg levels showed a gradual increase when the treatment was further continued and by the end of 120 days' treatment the urinary Mg levels had increased almost two-fold compared with the initial levels. A significant increase ($P < 0.01$) in urinary citrate levels over the pretreatment levels was observed after 30 days of treatment. Urinary citrate excretion increased significantly ($P < 0.001$) with further therapy for 60, 90 and 120 days. In contrast to Mg and citrate, combined supplementation with MgO and pyridoxine for 60 days significantly ($P < 0.01$) lowered the urinary oxalate excretion. The

Table 3 Effect of MgO and pyridoxine therapy on urinary Ca × Ox and Ca × P molar products, Ca/Mg and Ca/Ox molar ratios and calcium oxalate risk index of stone formers (means ± SD; $n = 16$)

Parameter	Day O	Day 30	Day 60	Day 90	Day 120
Calcium × oxalate	4.61 ± 2.81	3.87 ± 2.21	3.92 ± 2.18	2.83 ± 1.58[a]	3.06 ± 1.76
Calcium × phosphate	182.25 ± 133.51	165.80 ± 108.00	206.03 ± 116.19	192.31 ± 163.00	228.22 ± 210.00
Calcium/magnesium	4.96 ± 4.52	3.49 ± 2.94	3.49 ± 1.72	2.16 ± 0.93[a]	2.77 ± 1.86
Calcium/oxalate	9.85 ± 5.56	10.13 ± 5.10	15.17 ± 7.03[a]	16.22 ± 8.71[a]	22.71 ± 12.50[b]
CaOx-RI[c]	0.09 ± 0.04	0.07 ± 0.03	0.06 ± 0.03	0.05 ± 0.02[b]	0.05 ± 0.02[b]

[a] $P < 0.05$; [b] $P < 0.01$ for difference from corresponding value on day 0; [c] Calcium oxalate risk index (CaOx-RI) = $(Ca/Cr)^{0.71} \times (Ox/Cr) \times (Mg/Cr)^{-0.14} \times (Cit/Cr)^{-0.1}$

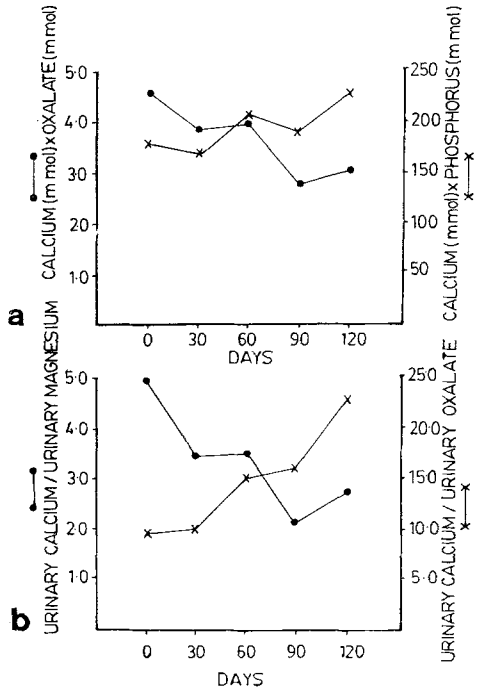

Fig. 1 Effect of MgO and pyridoxine supplementation on urinary **a** molar products of calcium × oxalate and calcium × phosphate; and **b** molar ratio of calcium/magnesium and calcium/oxalate

urinary oxalate levels showed a further decline after 90 and 120 days of treatment and by end of the therapy urinary oxalate levels were reduced by about 54% compared with the initial levels. Combined supplementation produced a moderate, but statistically non-significant, increase in urinary pH and calcium by the end of 120 days, while other urinary parameters, such as sodium, potassium, uric acid and phosphorus remained unaltered during the treatment.

Altered urine composition produced a significant ($P < 0.05$) decline in the molar product of calcium and oxalate after 90 days of MgO and pyridoxine supplementation (Table 3; Fig. 1a). The molar product of calcium and phosphorus remained unchanged throughout the study. The molar ratio of calcium to magnesium showed a gradual decline with the progress of treatment and as compared to the basal value this ratio was significantly ($P < 0.05$) lower after 90 days of treatment. In contrast, the molar ratio of calcium to oxalate increased steadily with increased duration of therapy (Table 3; Fig. 1b). Tiselius calcium oxalate risk index (CaOx-RI) calculated using the formula $(Ca/Cr)^{0.71} \times (Ox/Cr) \times (Mg/Cr)^{-0.14} \times (Cit/Cr)^{-0.10}$ [28], showed a gradual decline and had significantly ($P < 0.01$) decreased after 90 days of treatment (Table 3).

Discussion

The present study provides biochemical support to MgO · pyridoxine therapy for recurrent calcium oxalate urolithiasis. The combined dosage of MgO and pyridoxine · HCl administered in this study was the same as that used by Prien and Gershoff in 1974 [21]. A few investigators have used higher doses of MgO [2, 5] which have the disadvantage of significantly increasing urinary calcium levels [29].

Combined supplementation with MgO and pyridoxine significantly lowers urinary oxalate excretion, which is the major factor contributing to prevention of calcium oxalate crystallization. Both pyridoxine deficiency [18] and magnesium deficiency [22] in experimental animals have been shown to produce significant hyperoxaluria mainly due to enhanced endogenous production of oxalate. Pyridoxine supplementation in doses varying from 10 mg to 1 g per day by various investigators [7, 8, 17, 33], have demonstrated an overall beneficial effect on urinary oxalate excretion in hyperoxaluric recurrent calcium oxalate stone formers. Harrison et al. [9] have described a subset of idiopathic calcium oxalate stone formers with increased urinary excretion of both oxalate and glycolate, probably due to abnormal endogenous oxalate metabolism. Pyridoxine therapy administered to such patients significantly lowered urinary glycolate and oxalate levels in some but the response was not consistent [25]. Using molecular genetic techniques Danpure [4] has demonstrated significant enzymic heterogeneity in primary hyperoxaluria type I, which may in turn be responsible for heterogeneity at clinical level and responsiveness to pyridoxine therapy. Pyridoxine supplementation may decrease endogenous oxalate synthesis either by channelling glyoxylate to glycine or by maintaining the enzymes of oxalate biosynthesis, viz. glycolic acid oxidase (GAO) and glycolic acid dehydrogenase (GAD) at lower activity levels [17]. Magnesium supplementation lowers urinary oxalate excretion both by affecting its absorption and by regulating its

endogenous synthesis. Berg et al. [3] have indirectly illustrated that magnesium, like calcium, inhibits oxalate absorption possibly by forming magnesium oxalate complex. The hypercalciuric effect of magnesium supplementation [29] is indicative of parathyroid suppression, which may in turn lead to low intestinal calcium and subsequently to low oxalate absorption. Magnesium is a cofactor in the decarboxylation of glyoxylate by the glyoxylate oxidation cycle or α-ketoglutarate-glyoxylate carboligase [22]. An excess of magnesium might stimulate these reactions thereby making less glyoxylate available for conversion into oxalate. Thus the significant decrease in urinary oxalate excretion with combined supplementation of MgO and pyridoxine could be due to their additive effect on oxalate metabolism.

The combined therapy also had a significant effect on urinary excretion of magnesium and citrate, the well-known inhibitors of calcium oxalate crystallization. Magnesium oxide supplementation raised urinary Mg excretion by 1–2 mmol/day and citrate by 0.5–1.0 mmol/day. The increase in urinary citrate following MgO supplementation probably reflects the alkali-induced inhibition of renal tubular citrate reabsorption [24]. A moderate increase observed in urinary pH following MgO · pyridoxine supplementation is indicative of alkali load delivered by MgO. The alkalization effect of MgO as indicated by decreased urinary ammonium levels and increased urinary pH, leading to increased urinary citrate, has been reported in calcium oxalate stone formers [13]. Ogawa et al. [20] have reported a significant increase in 24 h urinary pH and citrate excretion in urolithitic rats following MgO administration.

The calcium × oxalate molar product is an important measure for calculating the risk of calcium oxalate precipitation and stone formation. The constant decline in this product during the therapy indicates low possibility of calculogenesis. As there were no changes in phosphorus excretion the calcium × phosphorus molar product remained unchanged throughout the supplementation period. The combined therapy produces a significant decrease in urinary oxalate excretion without any significant change in calcium excretion thereby steadily increasing the ratio of calcium to oxalate, which is less conducive to calcium oxalate precipitation. A high Ca/Mg ratio in association with hyperoxaluria is considered to be an important cause for the formation of urinary calculi [26]. Treatment with MgO increases the urinary Mg thereby producing a steady decline in the Ca/Mg quotient which further enhances its beneficial effect.

The therapeutic efficacy of combined supplementation with MgO and pyridoxine can thus be explained in terms of its effect on urinary lithogenic factors and crystallization inhibitors, which is in turn producing a significant decrease in the calcium oxalate risk index [28]. Combined supplementation of MgO (300 mg/day) and pyridoxine (10 mg/day) is a beneficial therapy for recurrent calcium oxalate stone formers, and it acts by creating a urinary environment of low calcium oxalate crystallization, growth and aggregation.

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