Effect of Daily MgO and Vitamin B₆ Administration to Patients with Recurring Calcium Oxalate Kidney Stones¹ ²

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Studies reported from this laboratory some years ago demonstrated that vitamin B₆ deficiency in rats and cats resulted in a marked increase in urinary oxalate (1, 2). This oxaluria was accompanied in rats by the formation of calcium oxalate renal stones similar in structure to those seen in humans and associated with secondary obstructive sequelae involving the lower urinary tract (3). The feeding of high levels of magnesium to vitamin B₆ deficient rats markedly reduced the formation of urinary stones, although the hyperoxaluria was not affected (4). At about the same time, it was shown (5) that renal calcium oxalate deposition in rats receiving 0.25% ethylene glycol in their drinking water could be completely prevented by diets high in magnesium and partially prevented by very high dietary levels of vitamin B₆. In view of these studies, it was decided to investigate the effects of daily oral administration of magnesium and vitamin B₆ on patients with histories of recurring calcium oxalate urolithiasis.

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EXPERIMENTAL

Male and female adult patients who had made two or more calcium oxalate renal stones yearly during the 2 years prior to being approached were used in this study. For all of the subjects studied, crystallographic examination of their calculi had been made by one of us (E. Prien). Approximately 50% of the subjects studied were patients of Dr. Prien, the others were patients of cooperating urologists in various parts of the country. Because of the serious nature of their disease, all patients had been hospitalized, sometimes repeatedly for complete medical examination, prior to being accepted in this study. Patients with hyperparathyroidism, renal tubular acidosis, and other conditions commonly associated with recurrent calcigenous stone formation were excluded from the study. A few of the patients did have transient urinary infections but no other urinary tract lesions demonstrable by pyelography.

Before being started in this program, two 24-hr urine samples were obtained from all subjects. In addition, two blood samples, drawn at least 24 hr apart, were obtained from most of the patients from the Boston area. The patients were asked to take two tablets, each containing 100 mg MgO, and one tablet containing 10 mg pyridoxine daily. This treatment did not produce looseness of the bowels except in an occasional patient. In addition to the medication, all patients were instructed to avoid milk as a beverage but allowed the use of milk or cream in other foods. Intakes of cheese and other high calcium foods were restricted. They were asked to drink 2 qt of water per day. Most of the sub-
jects had been asked to observe these dietary precautions prior to the study as a consequence of their disease. The collection of blood and urine samples was repeated after the subjects had been on the experimental regimen for a year. Urines were analyzed for calcium (6), magnesium (7), citric acid (8), oxalic acid (9), xanthurenic acid (10), phosphate-P (11), and pyrophosphate-P (12).

In addition, the ability of the urines collected to hold oxalate in solution was determined by an adaptation of the method of Miller et al. (13). This method consisted of adjusting the pH of the urines studied to 6 and their calcium content to 15 mg/100 ml, and then filtering them. To 5 ml of the urines were then added varying amounts of 0.005 M sodium oxalate and water to a final volume of 7 ml. The amount of oxalate solution needed to give a reading of 10 on a Coleman nephelometer scale was considered an index of the ability of the urine to hold oxalate in solution.

Sera were analyzed for magnesium (7), lipoproteins (14), and total cholesterol and β-cholesterol (15). Serum fractions analyzed for β-cholesterol were obtained by preparative ultracentrifugation at a solution density of 1.063 g/ml (14).

RESULTS

Thirty-six patients have been maintained in this study for at least 5 years. In our own series of cases, 15 patients have now been in the program 5 years. There was no recurrence of kidney stone in nine. Two patients, each produced one stone in their 4th year in the program. Another passed several calculi over the Christmas holiday in his 1st year when he stopped taking the pills, one stone the 2nd year, and one stone in the 4th year. He had passed 11 calculi in the year before therapy was instituted and over 300 in the 14 years prior to entering this program. A fourth patient, a very busy executive of a large company, passed one or two small calculi per year for 5 years, none since. A fifth patient with two existing small stones when the treatment was started showed no increase in their size for 2½ years, failed to come in for checkups after this period and stopped taking the drugs 6 months later. One and a half years later, one of the stones had grown considerably and caused symptoms resulting in an operation. One patient showed no improvement and continued to make stones.

In 21 cases maintained in the program for 5 years under the care of cooperating urologists, there was no stone recurrence or marked improvement (decreasing stone frequency) in 16. Some difficulty was encountered in determining exactly whether stones passed were newly formed stones or were pre-existing calculi because several of the patients had a number of calculi existing in their kidneys when treatment was started. Also, there was a question as to whether a stone had really been passed in several instances when symptoms occurred and no stone was recovered. Kidney-ureter-bladder films provided the only objective data in these cases. In five subjects there was failure. New stones were formed or existing stones grew larger. One of these patients kept on forming and passing calculi.

Table 1 shows the effects on urine and serum constituents of being in this program 1 year. These data indicate that the treatment used significantly raised urinary calcium and citric acid, and lowered urinary xanthurenic acid and serum magnesium. Urinary oxalic acid, magnesium, phosphate-P and pyrophosphate-P, and serum total and β-cholesterol were not significantly changed. Serum lipoprotein values were also obtained by ultracentrifuge analysis. There was a significant lowering in the S12–20 and S20–35 fraction, but not in the other lipoproteins measured.

Using the procedure described for measuring the ability of urines to hold calcium oxalate in solution, the average amount of 0.005 M sodium oxalate solution needed to reach the end point for 51 control urines was 1.3 ml. After a year, the urines of 45 of the 51 patients studied showed an in-
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creased ability to hold oxalate in solution. Of these, 31 had such an increased capacity to hold oxalate in solution that 2 ml of oxalate solution, the maximum used in our procedure, was not sufficient to reach the turbidimetric end point.

**DISCUSSION**

During the early part of this century, there was considerable interest in using magnesium salts in the treatment of urinary stone disease. Until recently, interest in the treatment and prevention of calcigenous stones by magnesium administration was mainly sustained by the work of Hammarsten. In 1929 she reported that the solubility of calcium oxalate in water was markedly increased by MgCl₂ (16). She also reported that she was able to prevent the formation of calcium oxalate urinary stones in rats by adding magnesium to their diets and that dietary magnesium decreased oxalate excretion in rats and human subjects (17).

De Albuquerque and Tuma (18) have also reported that the feeding of MgO to oxalate stone formers reduced their excretion of oxalic acid. In the present study, oxalate excretion was not significantly affected in a group of 50 patients receiving MgO and vitamin B₆ therapy daily for a year. On the basis of a large number of studies done in this laboratory, we would interpret any lowering of oxalate excretion by vitamin B₆ and MgO treatment as being related to the administration of vitamin B₆. It has been clearly shown in rats (1) and cats (2) that vitamin B₆ deficiency is accompanied by an increase in oxalate excretion. In unpublished studies, similar results have been obtained in rhesus and Cebus monkeys. In two studies done in a mental hospital on subjects receiving a common diet considered to be adequate in vitamin B₆, the administration of vitamin B₆ was accompanied by a marked decrease in oxalate excretion (19). An association between oxaluria and high urinary xanthurenic acid and low vitamin B₆ excretion levels in Burmese subjects has been suggested (20), and oxalate excretion has been reported as being significantly higher in poorly nourished Thai village children than in private school children in a nearby city (21).

Extensive studies on rats in this laboratory have never indicated that dietary magnesium affects oxalate excretion, although it protects against the deposition of calcium oxalate in the kidneys of vitamin B₆-deficient rats (4) or rats receiving ethylene glycol in their drinking water (5). The use of radioactive precursors of oxalate in rats supports the conclusion that their conversion to oxalate is probably not affected by dietary magnesium but is quite sensitive to dietary vitamin B₆ levels. Thus it would

**TABLE I**

**Effect of Daily MgO and Vitamin B₆ Administration on Urinary and Serum Constituents of Patients with Recurring Calcium Oxalate Renal Calculi**

<table>
<thead>
<tr>
<th>Urinary Constituents, mg/24 hr</th>
<th>No. of Patients</th>
<th>Control</th>
<th>After 1 Year of Treatment</th>
<th>SE of Mean Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>51</td>
<td>218.0</td>
<td>276.0</td>
<td>13.0*</td>
</tr>
<tr>
<td>Magnesium</td>
<td>51</td>
<td>79.0</td>
<td>87.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Citric acid</td>
<td>51</td>
<td>435.0</td>
<td>531.0</td>
<td>33.0*</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>50</td>
<td>33.9</td>
<td>34.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Xanthurenic acid</td>
<td>51</td>
<td>12.3</td>
<td>5.1</td>
<td>1.2b</td>
</tr>
<tr>
<td>Phosphate-P</td>
<td>25</td>
<td>849.0</td>
<td>821.0</td>
<td>87.0</td>
</tr>
<tr>
<td>Pyrophosphate-P</td>
<td>25</td>
<td>1.31</td>
<td>1.24</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum constituents, mg/100 ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>25</td>
<td>2.18</td>
<td>1.88</td>
<td>0.05*</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>25</td>
<td>277.0</td>
<td>262.0</td>
<td>10.0</td>
</tr>
<tr>
<td>β-Cholesterol</td>
<td>25</td>
<td>131.0</td>
<td>136.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 0-11</td>
<td>25</td>
<td>333.0</td>
<td>345.0</td>
<td>14.0</td>
</tr>
<tr>
<td>S1 12-20</td>
<td>25</td>
<td>54.0</td>
<td>32.0</td>
<td>6.6*</td>
</tr>
<tr>
<td>S1 21-35</td>
<td>25</td>
<td>31.0</td>
<td>20.0</td>
<td>3.5*</td>
</tr>
<tr>
<td>S1 36-100</td>
<td>25</td>
<td>62.0</td>
<td>55.0</td>
<td>11.0</td>
</tr>
<tr>
<td>S1 101-400</td>
<td>25</td>
<td>21.0</td>
<td>11.0</td>
<td>4.9</td>
</tr>
</tbody>
</table>

*P < 0.01.  
**P < 0.001.
appear that the role of magnesium in preventing calcium oxalate deposition in the rat urinary tract is not the result of an effect on the amount of oxalate excreted. This protective effect is obtained not only without a decrease in urinary oxalate but may be associated with an increase in urinary calcium (22). Increased urinary calcium following magnesium administration in animals and man has commonly been observed. In the present work, the groups of subjects studied excreted approximately 25% more calcium after receiving MgO and vitamin B₆ for a year.

A possible rationale for an effect of MgO and vitamin B₆ administration in protecting against calcium oxalate urolithiasis might involve an effect on the solvent characteristics of urine. Vermeulen et al. (23) and Miller et al. (24) have reported that a variety of metabolites found in urine are effective in increasing the solubility of calcium phosphate and calcium oxalate in water. Citrate and magnesium are particularly effective as solubilizers. Mukai and Howard (25) have reported that urine from stone formers, which calcified rachitic rat cartilage, becomes noncalcifying when magnesium is added to it. Du Mont and Nowak (26) found that the drinking of mineral water with a high magnesium content increased the colloid stability of urine from subjects with and without urinary stone disease. In previous studies from this laboratory it was observed that calcium oxalate stone patients with no history of urinary tract infection excreted less citric acid than normal subjects. Furthermore, vitamin B₆-deficient rats, which form calcium oxalate urinary calculi, excrete only a small fraction of the citric acid excreted by control rats. This decrease in citric acid was prevented by feeding vitamin B₆ or high dietary levels of magnesium (4).

The results of the present studies indicate that the capacity of the urines of 45 of 51 subjects studied to hold calcium oxalate in solution was increased by the experimental regimen. This increase was of sufficient magnitude so that with the method used for measuring the ability of urine to maintain calcium oxalate in solution, we were unable to measure calcium oxalate turbidity in the urines of 31 of the subjects after a year on the experiment. It seems unlikely that the change in the solvent characteristics of the urine from the patients studied can be explained simply on the basis of altered magnesium and citric acid content. There was not a statistically significant rise in urinary magnesium as a result of the treatment used. It is unfortunate that we were unable to determine the distribution of urinary magnesium in bound and ionic forms. The treatment used resulted in a significant increase in average urinary citric acid of about 100 mg/day. This would not entirely explain the increased solubility of calcium oxalate in the urine of the subjects. The excretion of pyrophosphate, which has been reported as being extremely active in inhibiting the formation of calcium deposits in vivo and in vitro (27), was not altered in the 25 subjects studied.

There have now been 36 patients with histories of recurring calcium oxalate kidney calculi who have received daily treatment with MgO and vitamin B₆ for at least 5 years. The problems in carrying on this type of experiment are often disheartening. Individuals with urinary stone disease often endure a great amount of pain. It is easy to enlist the cooperation of patients who have recently had an attack of stone disease. However, after a year or two without a further attack, their interest wavers and their cooperation becomes increasingly poor. Since in most individuals who form stones, calculi may only appear sporadically, any stone-prevention program must be evaluated over a long period of time. In this report we have not included clinical data on approximately 50 patients who dropped out of the study after 1–3 years, mostly because of their having no...
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It is impossible to maintain an accurate check on subjects to know whether they are following instructions. One must, to a great extent, depend on their word. Two subjects who continued to form stones after being put in this program later admitted that they had not taken their pills.

We are encouraged by the results obtained so far. Of 36 patients who have been maintained in this program for 5 years or more, 30 have shown no recurrence or decreased recurrence of stone formation. We recognize that only a much larger series of cases treated over a long period of time will determine the efficacy of this regimen.

There is no reason to believe that there is a common etiology in all cases of calcium oxalate urolithiasis. Therefore, it is not unreasonable that a prophylactic treatment might be extremely effective in some patients but not in others. Some people, instead of forming small numbers of large calcium oxalate stones, form large numbers of small stones which they pass. Because of the number of attacks they suffer, it is relatively easy to evaluate prophylactic measures for them. We have already in this report described such a case, a man who passed over 300 stones in the 14 years before entering this program, who now only passes an occasional small stone. Moore and Bunce (28) have recently reported two cases of individuals of this nature who passed 2–4 calculi/month. Oral administration of 420 mg of MgO/day protected both of them without any adverse reactions to the MgO. Cessation of therapy in one of these individuals for a month resulted in resumption of calculus formation.

Malkiel-Shapiro and Bersohn (29) have reported a dramatic clinical improvement in many cases of coronary heart disease following parenteral administration of MgSO₄, accompanied by reversion of abnormal serum lipoprotein values to normal. Parsons et al. (30) observed a similar effect of intramuscular MgSO₄ on patients with coronary heart disease associated with a marked reduction in serum cholesterol and \(\beta\)-lipoproteins. In rats (31) and monkeys (32) fed diets containing cholesterol, magnesium deficiency has been associated with the production of atherosclerosis, although only in the monkeys did the magnesium content of the diet affect the serum cholesterol levels. Vitamin B₆ deficiency has also been associated with the production of atherosclerosis in monkeys and dogs, and vitamin B₆-deficient monkeys and chicks show a greater degree of hypercholesteremia when fed cholesterol than control animals (33). In view of these observations, serum magnesium, cholesterol, and lipoproteins were determined in the present study on 25 subjects. The daily ingestion of MgO and vitamin B₆ for a year did not affect serum cholesterol values but resulted in a decrease in serum Mg and \(\beta\)-lipoproteins above S₁₂, particularly in the S₁₂–35 groups. Just what the serum changes observed in the present study mean is obscure. The reduction in serum lipoproteins is of some interest in that it may be relevant to the observations cited above.

**SUMMARY**

Patients with histories of recurring calcium oxalate renal stone formation have been given daily oral supplements of 200 mg of MgO and 10 mg of pyridoxine for extended periods of time. Thirty of 36 patients maintained on this program for 5 years or more have shown no recurrence or decreased recurrence of stone formation. After 1 year on this regimen, urines obtained from 51 patients showed a marked increase in their capacity to maintain calcium oxalate in solution, significantly raised calcium and citric acid levels, and decreased xanthurenic acid levels. No significant changes were observed in urinary magnesium, oxalic acid, phosphate-P or pyrophosphate-P values. Decreases in serum \(\beta\)-lipoproteins were also observed in a group of 25 of these subjects.
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REFERENCES


