Four years experience with magnesium hydroxide in renal stone disease*)

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Zusammenfassung

Mg ist seit vielen Jahren als Inhibitor der Ca-Oxalat-Steinbildung bekannt und wurde schon im Jahre 1810 als Prophylaktikum vorgeschlagen.

Patienten: 56 ambulante Patienten mit chronischem Steinleiden ohne Zeichen eines Mg-Mangels wurden behandelt. Vor der Therapie betrug die Steinhäufigkeit 0,8/Jahr.

Als *Kontrollen* dienten 43 Steinbildner ohne Behandlung.

Ergebnisse: Behandlung mit 500 mg $Mg(OH)_2$ täglich erhöhte das Urin-Mg um 30 bis 40 %. Da die hohe Ca-Ausscheidung unverändert blieb, normalisierte sich das Mg/Ca-Ausscheidungsmuster. Die Citrat-Ausscheidung im Urin stieg unter der Therapie an. Die Steinbildung nahm von 0,8 auf 0,08 Steine/Jahr ab, und 85 % der Patienten waren frei von Rezidiven, während die Kontrollen weiter Steine bildeten. Nebenwirkungen waren selten.

Schlußfolgerung: Die Mg-Therapie bei Ca-Oxalat-Steinen ist wirkungsvoll bei geringen Nebenwirkungen und führt nicht zu Magnesium-Intoxikationen.

Summary

Magnesium (Mg) is since many years a known inhibitor of the formation of calcium oxalate crystals and was already in 1810 proposed for prophylactic treatment in renal stone disease.

Subjects. From our out-patient stone clinic were 56 recurrent renal stone formers with no sign of Mg deficiency selected for therapy. Stone episode rate (SER) before therapy was 0.8 stones/y.

Controls. 43 stone formers from the clinic without medical therapy.

Results. Treatment with 500 mg $Mg(OH)_2$ daily increased urinary (dU) Mg with 30—40 %. As the high pretreatment dU-calcium (Ca) remained unchanged, the pretreatment low dU-Mg/Ca ratio was normalized. dU-citrate increased on therapy. SER decreased from 0.8 to 0.08 st./y., and 85 % of the patients were free of recurrence, while the controls continued their stone formation. Side effects were few.

Conclusions. Mg treatment in renal calcium stone disease is effective with few side effects and without signs of Mg excess.

Résumé

Le magnésium (Mg) est depuis plusieurs années, un inhibiteur connu de la formation des cristaux d'oxalate de calcium et il a été proposé dès 1810 pour le traitement prophylactique dans la lithiase rénale.

Sujets: 56 sujets formant des calculs avec rechute, sans signes de déficit magnésique ont été sélectionnés dans notre clinique urologique externe pour le traitement. La fréquence des épisodes de calcul (F.E.C.) avant le traitement était de 0,8 calcul/an.

Contrôle: 42 sujets formant des calculs, provenant de la clinique, sans traitement médical.

Résultats: Le traitement par 500 mg de $Mg(OH)_2$ par jour a accru (dU) Mg urinaire de 30 à 40 %. Quand dU Ca élevé avant le traitement est resté inchangé, le faible rapport dU Mg/Ca avant le traitement s'est normalisé — dU citrate s'est accru au cours du traitement. La F.E.C. s'est réduite de 0,8 à 0,08 calcul/an, et 85 % des patients ont été dépourvus de rechute alors que les contrôles continuaient leur formation de calculs. Les effets secondaires ont été minimes.

Conclusions: Le traitement par Mg dans la lithiase rénale est efficace, avec des effets secondaires minimes et sans signes d'excès de magnésium.

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Introduction

Already in the year 1810 [3] was magnesium proposed as prophylactic treatment against renal stone disease. Hammarsten showed in 1929 [8] that magnesium increased the solubility of calcium oxalate *in vitro* and she also proposed magnesium as treatment to prevent renal calcium stones. *Desmars* and *Tawashi* [6] demonstrated the greater solubility product for magnesium oxalate than for calcium oxalate and recently have magnesium been found to account for 20 % of the total inhibitory activity of calcium phosphate precipitation in whole urine [2].

Magnesium deficiency is not a common feature in renal stone patients but most stone formers have a low urinary excretion of magnesium in relation to calcium [11].

We have earlier demonstrated the clinical and metabolic effects with magnesium hydroxide treatment on patients with recurrent renal calcium stone formation after two [10] and three years treatment [12]. In this study we report the results of treatment with magnesium hydroxide in renal stone formers treated for up to four years. These results are compared with those obtained from a group of stone formers without prophylactic treatment.

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Subjects and methods

Stone formers. Fifty-six recurrent renal calcium stone formers without sign of magnesium deficiency were selected for therapy from our outpatient renal stone clinic. There were 42 males and 14 females with a mean age of 44 ± 14 (SD) years. The mean stone episode rate (SER) before treatment was 0.8 stones per year, i.e. the patients had passed altogether 460 stones during 550 patient years.

Biochemical investigations were performed after 1, 3 and 6 months and thereafter at regular 6 months intervals. A new X-ray of the urinary tract was taken before treatment and thereafter each other year.

Controls. Natural history of stones was also followed in 43 patients not on medical treatment, either because it was considered that their stone disease was not active enough for prophylactic treatment or because the patients themselves prefered to wait with treatment. There were 35 males and 8 females with a mean age of 45 ± 11 (SD) years. SER was calculated to 0.5 stones per year.

Methods. Serum and urinary magnesium and calcium were determined by atomic absorption. Serum and urinary inorganic phosphate was analysed with a molybdate complexing method including a dialysis step. All these electrolytes were analysed by standard techniques at the clinical chemistry laboratory of the hospital. Citrate was analysed by a citrate lyase method. Immunoreactive parathyroid hormone (PTH) concentrations in serum were measured by a radio-immuno assay measuring intact human PTH and C-terminal ⅔ of the molecule [15].

Results

Serum and urinary data in renal stone formers are summarized in Table 1.

Effects on magnesium and calcium. Initially there was a slight increase of the serum magnesium, which persisted during the first year but thereafter returned to the pretreatment level. Urinary magnesium excretion was raised by 1.5 to 2.0 mmol/24 h urine on treatment (Table 1). Serum calcium decreased gradually during the four years of follow up. No changes were observed in the urinary calcium excretion (Table 1).

Effects on urinary magnesium/calcium ratio. As the urinary output of magnesium increased, but not the calcium output, the urinary magnesium/calcium ratio increased and approached the value found in healthy subjects [5].

Effects on phosphate. Serum phosphate decreased gradually and was significantly lower from two years treatment and thereafter. No changes were observed in the urinary phosphate excretion.

Effects on parathyroid hormone. Serum PTH was analysed in 33 patients after three years treat-

Tab. 1: Biochemical findings in 56 renal calcium stone formers treated with magnesium hydroxide.

	Before therapy 0	On therapy (months) 6	12	24	36	48
Serum magnesium (mmol/l)	0.83 ± 0.06	0.85 ± 0.01*	0.85 ± 0.01*	0.82 ± 0.06	0.82 ± 0.06	0.82 ± 0.07
Urinary magnesium (mmol/24h)	4.5 ± 1.5	6.0 ± 2.2**	5.9 ± 2.3**	6.5 ± 2.2**	6.1 ± 2.5**	6.6 ± 2.2**
Urinary calcium (mmol/24h)	6.9 ± 2.3	6.8 ± 2.9	6.8 ± 3.0	6.9 ± 2.9	7.1 ± 3.5	6.2 ± 2.2
Urinary magnesium/calcium	0.69 ± 0.21	0.93 ± 0.31**	0.91 ± 0.29**	1.05 ± 0.48**	1.02 ± 0.62**	1.13 ± 0.44**
Serum calcium (mmol/l)	2.48 ± 0.12	2.43 ± 0.10*	2.43 ± 0.08*	2.42 ± 0.09***	2.42 ± 0.09***	2.41 ± 0.09***
Urinary phosphate (mmol/24h)	28.7 ± 8.8	28.8 ± 10.3	29.8 ± 9.3	27.9 ± 8.9	26.5 ± 9.3	26.6 ± 10.0
Serum phosphate (mmol/l)	0.99 ± 0.19	0.94 ± 0.22	0.96 ± 0.18	0.92 ± 0.18*	0.89 ± 0.17*	0.91 ± 0.16*
Serum PTH (arbitrary units/l)[1]					0.76 ± 0.39****	
Urinary citrate (mmol/24h)	2.6 ± 1.4			3.0 ± 1.3*****		
Number of patients	(56)	(56)	(56)	(53)	(42)	(33)

* $p < 0.05$ compared with pretreatment values
** $p < 0.001$ compared with pretreatment values
*** $p < 0.01$ compared with pretreatment values
**** $n = 33$;
***** $n = 40$; $p < 0.01$
[1]) ref values 0.4—1.2 arbitrary units/l

ment and was found to be unchanged and within the normal range in all patients.

Effects on urinary citrate. The average urinary citrate excretion increased in 30 of the 40 investigated patients and was on treatment close to the value found in healthy subjects (3.1 ± 1.2; mean ± SD, mmol/24 h) [16].

Clinical effects. Fifty-three out of 56 patients have been on treatment for at least two years and 33 for at least four years. Eight of these 56 patients have during treatment experienced stone recurrence, i. e. 86 % have been free of recurrence (Fig. 1). SER was reduced from 0.8 to 0.08 stones per patient and year.

In the control group, 15 out of 43 patients had formed new stones after two years observation and 15 out of 37 after three years without prophylactic treatment (Fig. 1).

Clinical side effects. Six patients failed to return for follow-up of unknown reasons and another few discontinued the therapy because of gastro-intestinal discomfort.

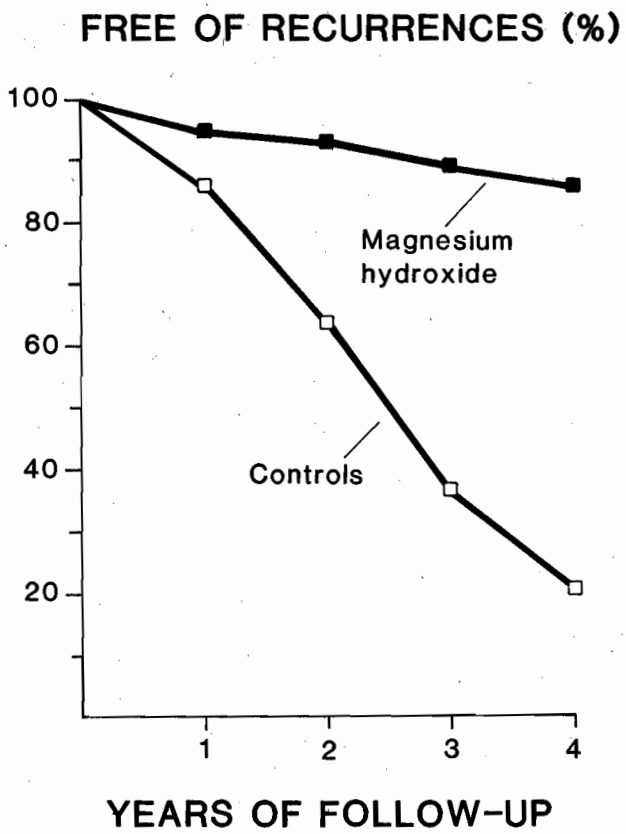

Fig. 1: Recurrence rate in renal stone formers treated with magnesium hydroxide or only given general advice.

Discussion

The clinical results after four years treatment with magnesium hydroxide in recurrent renal stone formers are in agreement with our earlier experiences reported after two [10] and three years treatment [12]. Eighty-six per cent of the patients are still free of recurrence after four years and the mean stone episode rate decreased from 0.8 to 0.08 stones per patient and year.

One possible explanation for the clinical effects with magnesium might be the observed inhibitory activity on calcium crystallization in urine both shown in vitro [6] and in vivo [2]. The increased magnesium output and unchanged calcium output in the urine shifts the situation in the urine to be less favourable for crystallization aggregation and stone growth. Also another inhibitor in the urine, urinary citrate, was found to be increased on magnesium therapy. Similar experiences have been demonstrated by *Gershoff* and *Prien* [7], using magnesium oxide and vitamin B_6. *Albuquerque* and *Tuma* [1] also reported a decreased urinary excretion of oxalate in stone formers treated with magnesium oxide. However, urinary oxalate has not been followed in our patients.

Clinical adverse effects were few on therapy. Only a few patients discontinued the treatment due to gastro-intestinal discomfort and another few temporarily reduced the dose because of mild intestinal disturbance. No other clinical side effects were observed.

The possibility of developing a hypermagnesemia during long term treatment with magnesium must of course be considered. However, during these four years on treatment no patient had any serum magnesium value above the normal upper limit or any symptom due to hypermagnesemia.

The decrease in both serum calcium and serum phosphate, together with an unchanged urinary excretion of both ions, remains unclear. *Melnick* et al. [14] could not demonstrate any change in serum or urinary calcium and phosphate during treatment with magnesium oxide. *Gershoff* and *Prien* [7], however, showed a slight increase in urinary calcium output but an unchanged urinary phosphate excretion using magnesium oxide. Short term treatment with magnesium hydroxide (three months) did not demonstrate any change in urinary excretion of calcium or phosphate or in serum calcium [13]. *Heaton* and *Parsons* [9] used oral supplement with magnesium acetate and showed an increased urinary calcium output and an unchanged serum calcium level. *Briscoe* and

Ragan [4] demonstrated similar results using oral supplement with magnesium hydroxide. Both studies were performed during short-term treatment. It is suggested that an increase in oral intake of magnesium hydroxide in the diet induces changes in the activity of the parathyroid glands during the day with a compensatory reversal during the night, resulting in greater oscillations in secretory activity than normal. An overall lower activity of PTH might explain our observations although the PTH level was normal in 33 patients studied after three years treatment.

Prophylactic treatment with magnesium hydroxide reduced stone recurrence rate in renal calcium stone formers. Side effects were few but possible adverse effects as the observed decrease in serum calcium and serum phosphate during long term treatment have to be further evaluated. No signs of hypermagnesemia were observed.

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Unbekannt verzogen?

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