Drug Invest. 3 (3): 135-140, 1991
0114-2402/91/0003-0135/$03.00/0

DRI1 028a

Steady-State Serum Concentration and Therapeutic (Target) Concentration Range During Oral Magnesium Therapy

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Summary Signs of magnesium toxicity appear at serum magnesium concentrations of 1.5 mmol/L. The reference range is 0.75 to 0.93 mmol/L and intraindividual variation in healthy subjects is negligible. Magnesium deficiency and marginal deficit are widespread, the latter being reflected in high intraindividual variations in serum magnesium concentration, and the former in a consistent decrease in serum levels. The distribution of magnesium can be described by a 2-compartment system. The purpose of this study was to estimate the time required to achieve steady-state concentrations (i.e. saturation of metabolism) after oral ingestion, which is safer than parenteral administration unless frequent monitoring is possible.

In an open study, 10 hypomagnesaemic patients consecutively admitted to the Back Rehabilitation Unit, Ichilov Hospital, with musculoskeletal pain of nonmalignant origin were given 2 to 6 oral magnesium hydroxide tablets (125 to 750mg of Mg^{++}) daily depending on tolerance, for 6 months, followed by 2 tablets daily until a steady-state serum concentration was achieved.

The initial serum magnesium concentration was 0.703 ± 0.008 mmol/L, measured by atomic absorption spectrophotometry, and at steady-state was 0.910 ± 0.006. The mean 24-hour urinary magnesium was initially 3.80 ± 2.34 mmol/24h, increasing to 5.70 ± 1.14 mmol/24h. Mean time to achieve steady-state was 12.4 ± 6.2 (range 3.5 to 20) months. The only adverse effect, apart from diarrhoea at high doses, was a reduction in serum phosphate concentration after 9 months in 1 patient, and after 12 months in a further 2 patients. It is suggested that the range of 0.82 to 1.06 mmol/L serum magnesium concentration observed on saturation of metabolism should serve as a basis for defining the target range of serum magnesium concentrations in magnesium therapy.

The magnesium ion has been recommended for treatment of alcohol-related disease (Flink 1969) including alcohol encephalopathies (Stendig-Lindberg 1974), of epilepsy (Flink 1969; Stendig-Lindberg & Hultman 1980) and neuromuscular excitability (Durlach 1988), and more recently used in the treatment of cardiovascular diseases (Iseri 1986; Rasmussen et al. 1986; Smith et al. 1986: Weiss et al. 1986), to prevent kidney stone formation (Johansson et al. 1981a), and as an adjuvant in the treatment of diabetes (Johansson et al. 1981b). Flink et al. (1954) used parenteral magnesium sulphate for treatment of alcoholism and epilepsy. Controlled oral treatment using magnesium hydroxide was initiated by Fletcher et al. (1960), and since 1963 has been used by the present author (Stendig-Lindberg 1974) and later by Johansson et al. (1981a,b), Kinnunen et al. (1989) and others.

For clinical studies it is necessary to consider magnesium as a drug, the distribution of which is described by a 2-compartment system. This approach has been implied in the work of Classen et al. (1983) in the rat, and Lucker et al. (1983) in humans, which showed that the filling level of the peripheral compartment determines the extent to which magnesium is absorbed (i.e. its bioavailability) or eliminated; urinary excretion rises when the peripheral compartment is saturated. This is supported by Morris et al. (1987) who showed that 56.6 mmol of an oral cathartic dose of magnesium sulphate was absorbed to a limited and variable extent in 6 healthy men, and by Rasmussen et al. (1988) who found that 4.6% of an intravenous loading dose of 30 mmol magnesium sulphate was retained in healthy subjects, while in coronary patients in whom magnesium deficiency was expected, 36% was retained.

According to Brodie and Feely (1988), a steady-state concentration of a drug signifies the saturation of metabolism. In strict terminology, however, metabolism means a process of changing a drug from its original form, while magnesium only undergoes ionisation. Magnesium, either ionised or chelated to substrates, enzymes or cell constituents, exerts enzyme kinetic, thermodynamic and other biological effects (Gunther 1981) and probably plays a regulatory role within the cell in various metabolic processes (Grubbs & Maguire 1987). When applied to magnesium it is therefore more correct to define the steady-state concentration of magnesium in serum as that which signifies the presence of an adequate intracellular magnesium content (Stendig-Lindberg et al. 1977) and a state of balance of absorption/ elimination processes.

The time needed to reach steady-state will depend on the vehicle and dose of magnesium used and the degree of magnesium deficit. In addition, the rate of magnesium accumulation in tissue, which is dependent on the functional state of the receptor protein-binding sites (Feely & Brodie 1988) and the rate of binding of magnesium to muscle protein and cell membrane magnesium-binding sites, will determine the time needed to saturate the peripheral compartment.

The steady-state concentrations obtained on controlled oral magnesium treatment could suitably serve as a basis for extrapolating the therapeutic range, or the target range of concentrations (Brodie & Feely 1988), i.e. that within which one anticipates clinical improvement without toxicity. Defining a target range could serve as a useful guideline in therapeutic strategy. This is of special importance in view of the wide prevalence of magnesium deficiency and marginal magnesium deficit occurring even in apparently healthy subjects (Marier 1982; Stendig-Lindberg et al. 1983) which might necessitate wide use of oral magnesium therapy in the future. Thus, the purpose of the present study was to estimate the time required to achieve steady-state following oral administration of magnesium hydroxide.

Materials and Methods

10 female hypomagnesaemic patients (serum magnesium < 0.75 mmol/L), consecutively admitted to the Back Rehabilitation Unit of Ichilov Hospital with complaints of musculoskeletal pain of nonmalignant origin, who had normal serum creatinine concentrations and no history of kidney disease, who were free from hypotension, atrioventricular block and myasthenia gravis and were aged 41 to 66 years (mean 54.9 ± 7.7), were included in an open study. All patients were treated with magnesium hydroxide ('Milk of Magnesia', Mazor, Israel) in oral tablets, each containing 125mg Mg^{++}.

Dose and Compliance

The patients were first given 2 magnesium hydroxide tablets to chew (on an empty stomach) at bedtime. If diarrhoea occurred they were instructed to stop the treatment for 8 days and restart it with only 1 tablet daily. The dose was titrated upwards (Montgomery 1987) according to individual tolerance, to reach a maximum of 2 tablets 3 times daily (750mg Mg^{++}) chewed and swallowed on an empty stomach (to prevent formation of insoluble complexes). This dose was given for 6

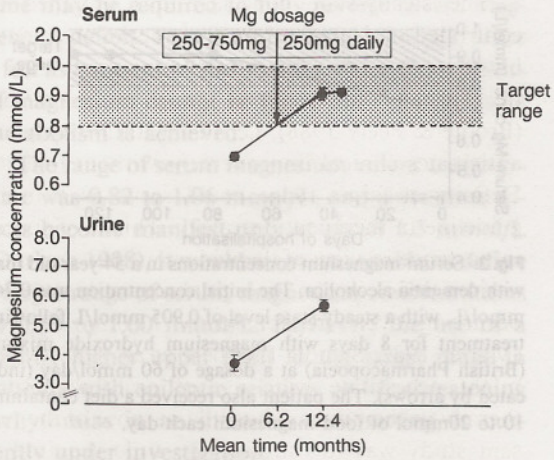

Fig. 1. Mean serum and urine magnesium concentrations in relation to duration and dosage of oral magnesium treatment. Note: the steady-state serum magnesium concentration was achieved after a mean of 12.4 months.

months, after which patients received 2 tablets once daily.

The patients filled a compliance chart for the first 3 months, and returned all empty medicine containers to the clinic so that the amounts taken could be recorded throughout the study. Steady-state serum magnesium concentrations were considered to be reached when values lay within the reference range (0.75 to 0.93 mmol/L) and were virtually identical on repeated measurement.

Laboratory Measurements

Blood was sampled from the median cubital vein, using brief stasis, at 8am, after an overnight fast. Serum and 24 hour urinary magnesium concentrations were estimated in duplicate on a Perkin Elmer absorption spectrophotometer No. 305 A (Stendig-Lindberg et al. 1984) before and during the study. For calculation of urinary magnesium levels in 24 hour urinary samples, 2 samples were collected within a 7-day interval, and the mean of the 2 values used. Other laboratory parameters were examined in a standard manner.

Statistical Analysis

Means and standard deviations were calculated for serum magnesium concentration before treatment, throughout the study, and after achievement of steady-state. Means of the 2 consecutive urinary magnesium measurements were calculated for each estimation. Mean time of treatment until steady-state was achieved was calculated.

Results

Using oral magnesium hydroxide tablets in a dosage of 250 to 750mg daily for the first 6 months, and 250 mg/day thereafter, the mean time to steady-state was 12.4 ± 6.2 months (range 3.5 to 20).

The serum and urinary magnesium values before treatment and after reaching steady-state are shown in figure 1. The range of serum magnesium values found at steady-state (0.82 to 1.06 mmol/L) could serve as a basis for defining a target range of magnesium concentrations, particularly as the upper value lies below 1.50 mmol/L: this is the value at which toxic symptoms due to excess Mg^{++} begin to appear (fig. 2).

The only side effect observed in the treated

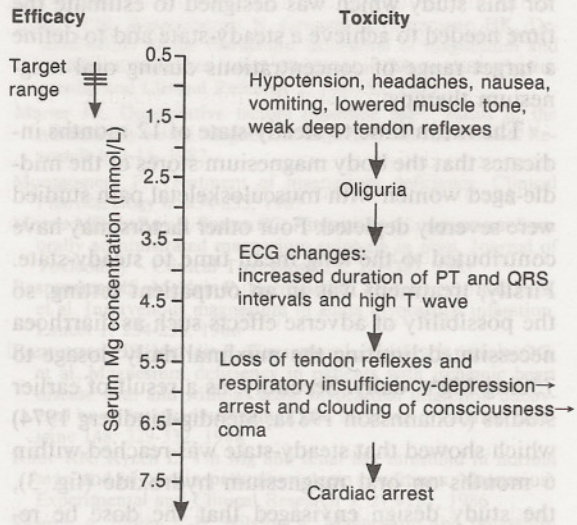

Fig. 2. Relation of efficacy of magnesium to toxicity. Note the suggested target range of 0.80 to 1.00 mmol/L marked on the left.

patients was lowering of serum phosphate concentrations in 3 patients (30%); in 1 patient after 9 months, and in 2 additional patients after 12 months.

Discussion

Pharmacokinetic studies on magnesium have been reviewed by Weiss et al. (1986) and by Durlach (1988). Nevertheless, many questions remain unanswered in terms of finding an optimum vehicle for the ion, definition of an optimal dosage regimen, and estimating the length of time required for adequate treatment.

The potential toxicity of high dose magnesium necessitates frequent monitoring of serum and urinary magnesium levels during parenteral administration, preferably in an intensive care setting with the dose limited to 720mg Mg^{++}/12h (the transport maximum of the kidney) [Rude & Ryzen 1986]. Logistically, it is simpler to use the oral route wherever possible.

Tablet formulations of magnesium hydroxide are not ideal preparations because the salt is an antacid. However, it is widely available and relatively safe. Therefore, it was the vehicle of choice for this study which was designed to estimate the time needed to achieve a steady-state and to define a target range of concentrations during oral magnesium therapy.

The mean time to steady-state of 12 months indicates that the body magnesium stores of the middle-aged women with musculoskeletal pain studied were severely depleted. Four other factors may have contributed to the long mean time to steady-state. Firstly, treatment was in an outpatient setting, so the possibility of adverse effects such as diarrhoea necessitated limiting the maximal daily dosage to 750mg Mg^{++} daily. Secondly, as a result of earlier studies (Johannsson 1981a; Stendig-Lindberg 1974) which showed that steady-state was reached within 6 months on oral magnesium hydroxide (fig. 3), the study design envisaged that the dose be reduced to 250mg Mg^{++} daily after the first 6 months. Estimating that the bioavailability of orally administered magnesium salts is 33% (Walser 1957)

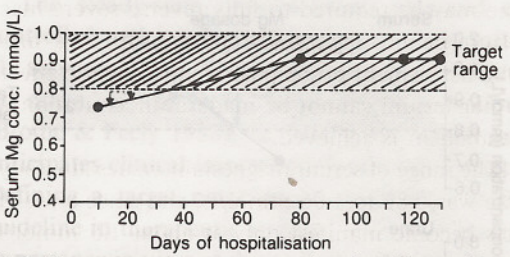

Fig. 3. Serum magnesium concentrations in a 54-year-old man with dementia alcoholica. The initial concentration was 0.740 mmol/L, with a steady-state level of 0.905 mmol/L following treatment for 8 days with magnesium hydroxide mixture (British Pharmacopoeia) at a dosage of 60 mmol/day (indicated by arrows). The patient also received a diet containing 10 to 20mmol of food magnesium each day.

to approximately 50% (Cook 1973), 80 to 125mg magnesium absorbed daily represents mere maintenance and not a therapeutic dose. It would primarily supplement the inadequate daily intake in food (Marier 1982), which in Israel amounts to 200 to 300mg magnesium daily (Stendig-Lindberg et al. 1983), leaving only a small fraction for filling the peripheral compartment. Use of higher doses beyond the first 6 months would have considerably shortened the time to steady-state.

Ebel et al. (1975) suggested a lower bioavailability in older subjects; the high mean age of the patients studied could constitute the third factor contributing to the long time to steady-state in our study. Finally, the bioavailability of magnesium hydroxide in comparison with other salts may be a contributory factor. Cook (1973) compared the bioavailability of insoluble magnesium salts in Sprague-Dawley rats and found 65% for carbonate, 61% for chloride and 58% for oxide salts. The water-soluble sulphate and insoluble silicates showed 53 to 54% absorption, estimated by measuring plasma, urine and femural magnesium content. Classen et al. (1978), on comparing magnesium salts in the cat, reported the highest bioavailability for magnesium aspartate hydrochloride. Further research is therefore needed to find an optimal vehicle for the clinical use of oral magnesium.

In the meantime, it is important to note that, as shown in the present study, a very considerable

time may be required to fully reverse severe magnesium deficit. This is an important finding, since a full assessment of the possible therapeutic effects of magnesium cannot be made until saturation of metabolism is achieved.

The range of serum magnesium values at steady-state was 0.82 to 1.06 mmol/L, and since toxic effects become manifest only at about 1.5 mmol/L (Durlach 1988), it would seem reasonable to define a target range of serum magnesium concentrations as 0.80 to 1.00 mmol/L. However, the use of a slightly higher upper limit to the target range in patients with epileptic seizures or life-threatening arrhythmias in an intensive care setting, is currently under investigation.

The mean urinary magnesium level of 5.7 ± 1.14 mmol/L (n = 10, range 4.3 to 7.7) found at steady-state indicates that this is the approximate urinary magnesium level to be expected in apparently healthy subjects who are not magnesium deficient. Since there is a positive correlation between urinary magnesium and the intracellular content (Sjogren et al. 1987; Stendig-Lindberg et al., unpublished data) urinary magnesium may serve as an index of the intracellular status of the ion. A mean urinary value of 6.0 mmol/24h should signify the presence of adequate body stores in subjects not receiving diuretics, glucose, alcohol or other magnesium loss-promoting agents (Durlach 1988) and not suffering from 'magnesium-losing kidney' (Gill 1988).

Acknowledgement

The author wishes to thank Nydia Chesler for her secretarial assistance.

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