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# Magnesium therapy in deficiency – some pharmacological aspects

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## INTRODUCTION

The early recognition of indications for magnesium (Mg) treatment requires awareness of the signs and symptoms of Mg deficiency and routine laboratory screening which should consist of at least two serum magnesium concentration (S-Mg) measurements, spaced out over e.g. 7-10 days. Whenever possible, two 24 hr samples of urine should be monitored for urinary Mg concentration/24 hrs (U-Mg) as well. Unfortunately, investigations of intracellular Mg content are not readily accessible in routine clinical daily work. Also, a correct interpretation of the routine laboratory findings to gauge the degree of depletion, if any, poses certain problems (Stendig-Lindberg et al, 1983) which make the decisions concerning therapy very challenging (Durlach, 1988). It is for this reason that some theoretical aspects of Mg therapy, the choice of a suitable Mg vehicle, dosage, length of treatment and safeguards against overdosage will be discussed in light of the pharmacological concepts which may help to guide us in the practical clinical issues associated with Mg treatment.

## THEORETICAL ASPECTS

Although Mg is an endogenous substance, many pharmaceutical products mimic endogenous substances, therefore Mg could abide under similar pharmacokinetic and pharmacodynamic laws. For practical purposes, it would appear useful to relate to Mg as to those drugs, the distribution of which is described by a two compartmental system, the central compartment (i.e. the circulation and highly vascular organs, via which the entry and the elimination of a drug takes place) and the peripheral compartment (muscle, bone, fat etc.). This approach has been implied in the work of Classen et al (1982) in the rat and Lücker et al (1983) in man which showed that the filling level of the peripheral compartment determines the extent to which Mg is absorbed (i.e. its bioavailability) or eliminated; the urinary excretion rising when the peripheral compartment is saturated. It is also indicated in the recent studies of Morris et al (1987) showing that a 56.6 mmol of oral cathartic dose of $MgSO_4$ is absorbed to a limited and variable extent in 6 healthy men, or the study of Rasmussen et al (1988) which shows that i.v. loading dose of 30 mmol $MgSO_4$ gives 4.6% retention in 10 healthy probands, while 36% is retained in coronary patients in whom Mg deficiency is anticipated.

With many drugs, the time it will take for the peripheral compartment to fill depends on the rate of accumulation in tissues, the functional state of the

receptor protein binding sites and the duration of action of the biological processes which they influence (Feely and Brodie, 1988).

If we were to relate to Mg in these terms, we would have to anticipate a lag between the onset of Mg medication and the clinical effect which will depend both on the rate of filling of the various tissues of the peripheral compartment which we can call the macrofactor and the duration of action of the various intracellular and membrane related biological systems in which Mg takes part: the microfactor.

The consequence of adopting such a concept is that we may find some guidelines for dealing with Mg therapuetics. Since we can not expect a simple dose-effect relationship, it may be helpful, after having chosen a Mg vehicle, to start with a low dose and titrate upwards (Montgomery, 1987) in a trial and error fashion (as in the cases presented below), until an optimal dose and duration are found. Another useful guideline is to set as our therapeutic goal to ensure to achieve a steady state concentration. A steady state concentration of a drug in the circulation signifies the saturation of metabolism (Brodie and Feely, 1988). This aim enables us, with the help of circulating concentration (in our case; S-Mg), to gauge the intracellular state of Mg, whenever more sophisticated intracellular monitoring is not possible. Obviously, 24 hrs urinary Mg concentration monitoring, by adding information on elimination, can offer further help.

Brodie and Feely (1988) introduce a term "target range" of concentrations, by which is meant a range of concentrations in which clinical improvement is anticipated, without toxicity. In the author's knowledge we have not yet discussed the target range for S-Mg before, so it is proposed that we assume a target range of concentration of 0.800-1.000 mmol/l(Fig. 1), on the following grounds.

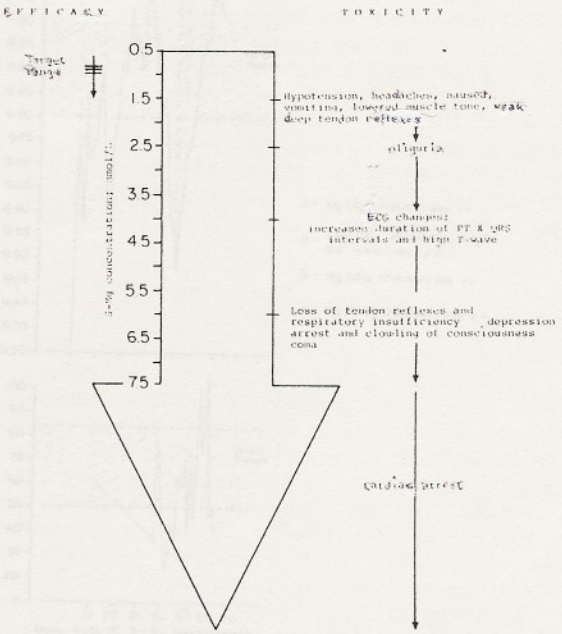


Fig. 1. Efficacy and toxicity of Mg and the target range.

In the literature, the mean S-Mg, globally, is roughly 0.800-0.900 mmol/l for healty populations. The reference value is based on the assumption, that in normal population, the concentrations will fall around the mean, within the range of $\pm$ 2 SD. But we know that the range of S-Mg in health is very narrow (Seelig and Berger, 1974) and that the reference value based on the calculation of $\bar{x} \pm 2SD$, often leaves us with a lower border value of the range which is close to, or below

.700 mmol/l; a concentration below which there is a threat to the membrane integrity and the preservation of intact intracellular content of Mg and other essential cell constituents (Stendig-Lindberg et al, 1977 and Günther, 1981).

To illustrate by an example: in the Israeli apparently healthy non-smokers and non-addicts ($\bar{x}$ 0.840, SD 0.060 mmol/l, n=10, age 40-52 yrs, mean, 44 yrs; Stendig-Lindberg, 1988; unpublished data) the addition of 2 SD to the mean gives 0.962 mmol/l as the upper border of the reference value, which is acceptable and when rounded up gives 1.000 mmol/l. This value, still safe and unaccompanied by signs of toxicity (Fig 1) can be safely accepted as the upper border of the target range. However, if we deduct 2 SD from the mean we get 0.720 mmol/l which is even by definition of hypomagnesaemia, used by the author (i.e. $\leqslant$0.73 mmol/l), too low and too close to the critical threshold value of 0.700 mmol/l (Günther, 1981). Therefore, the lower border of the target range proposed, can only be based on the substraction of 1 SD value alone from the mean, giving 0.780 mmol/L, which rounded up gives 0.800 mmol/l. The proposed values for the target range of U-Mg are derived from a group of 12 apparently healthy non-smokers, non addicts, aged 45-70 years (mean, 40 yrs), who were on a long term magnesium maintenance medication. These subjects, who were in a steady state, had a mean U-Mg of 6.67, SD, 1.70, mmol/24 hrs, n=12 (Stendig-Lindberg, 1988; unpublished data). It would appear that in order to arrive at an "ideal" desirable U-Mg target range, it would be advisable to use this mean $\pm$ 1 SD only. This gives a range of 5.00-8.40 mmol U-Mg (Fig 2).

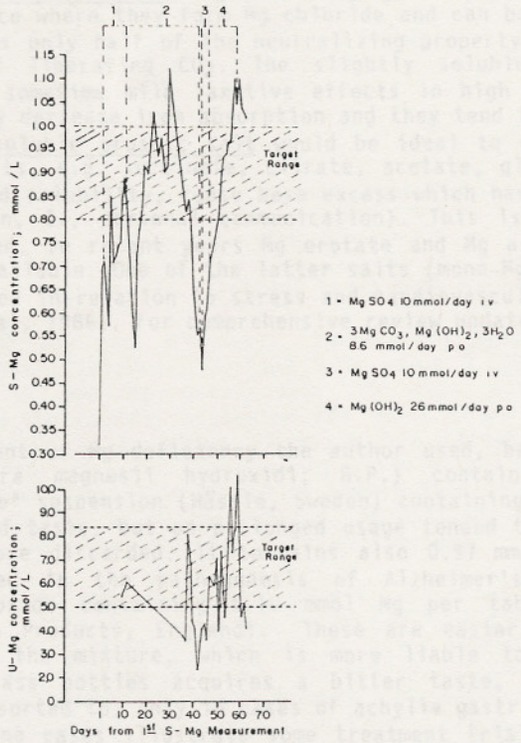


Fig. 2. Case No 1., Comparison of 3 Mg vehicles.

## CHOICE OF Mg VEHICLE

Faced with severely ill alcoholics in 1963, the author was confronted with the difficulty of choosing a suitable Mg vehicle. Flink (1954) and Vallee et al (1960) had used parenteral $MgSO_4$, prior to that time, and oral Mg therapy was used by Fletcher et al (1960) and Durlach (1961). I.m., or i.v. routes should be used only under conditions allowing for frequent monitoring of serum and urinary

magnesium concentration. Since hypermagnesemia which may result from overdosage may become life-threatening (Fig 1), magnesii sulfas sterile solution added to intravenous infusion, is indicated only in life-threatening conditions, or conditions resembling those of an intensive care unit. The dosage was proposed by Flink (1969) and applies only when kidney functions are normal. Since the right conditions for parenteral therapy were lacking, a choice had to be made between a variety of Mg salts available for oral usage; some inactive as the trisilicate and contraindicated because of reported risk of silica kidney stone formation, some soluble, but contraindicated because of strong laxative properties, see below.

The soluble inorganic salts: 1) Phosphate, although it has the advantage over the carbonate and oxide of not causing systemic alkalinization, could possibly disturb the calcium phosphate balance. Long term therapy would therefore need to be supervised by an endocrinologist. 2) The sulphate has the disadvantage of being highly laxative. 3) In cases of achylia gastrica the chloride salt is the only alternative. The chloride is customarily used in fluid form because the salt is highly hygroscopic. It is difficult, however, to mask its taste in soluble preparations and it may also give rise to gastric symptoms. In addition, as shown later in muscle tissue biopsy in man, the intracellular $Cl^-$ content is significantly raised in Mg deficiency (Stendig-Lindberg el at, 1977), so it would appear prudent to use this salt mainly in cases of achylia gastrica.

Insoluble inorganic salts: Mg oxide, Mg hydroxide, Mg carbonate are soluble in the gastric juice where they form Mg chloride and can be well absorbed thereafter. Mg carbonate has only half of the neutralizing property of the oxides and has the disadvantage of liberating $CO_2$. The slightly soluble and alkaline oxide and hydroxide have sometime mild laxative effects in high dosage, but seldom in low dosage. They may decrease iron absorption and they tend to bind to phosphates.

A neutral soluble organic salt would be ideal to use for Mg supplementation but organic salts, e.g. succinate, citrate, acetate, gluconate, lactate, although they have a good solubility, cause base excess which have to be eliminated via the kidneys (Sjogren, J., personal communication). This is a disadvantage when high dosage is needed. In recent years Mg orotate and Mg aspartate salts have become commercially available. One of the latter salts (mono-Mg L-aspartate HCL) has been widely researched in relation to stress and cardiovascular disease (Classen et al, 1980, Weiss et al, 1986). For comprehensive review update, see Durlach (1988).

## TRIAL AND ERROR

For the treatment of Mg deficiency the author used, beginning 1963, 1) Mg $(OH)_2$ mixture (mistura magnesii hydroxidi; B.P.) containing 1.20 mmol/ml Mg 2) "Novalucol Forte" suspension (Hässle, Sweden) containing 0.80 mmol/ml Mg. It had a better tolerated taste, but on prolonged usage tended to give rise to nausea, its use was therefore discarded. It contains also 0.97 mmol/ml aluminium, only much later implicated in the pathogenesis of Alzheimer's disease. 3) Tablets of magnesium hydroxide containing 5.10 mmol Mg per tablet ("Milk of Magnesia"; Sterling Health Products, England). These are easier to administer and better tolerated than the mixture, which is more liable to cause diarrhoea, and on standing in glass bottles acquires a bitter taste, difficult to mask. 4) Mg chloride was resorted to, only in cases of achylia gastrica.

The following cases illustrate some treatment trials using vehicles 1 and 2, and in case No.1, also, Mg $SO_4$ infusion and Mg carbonate:

Case no. 1. 76 yr old female. Diagnosis, hyperparathyroidism. Initial S-Mg is very low; 0.320 mmol/l. Mg $SO_4$ infusion ("Addex", Pharmacia, Sweden), 10 mmol Mg daily, was given over 10 days followed by oral administration of Magnesii Carbonas Levis (B.P.), 8.6 mmol daily over 31 days (Fig. 2; 1 and 2). The latter was accompanied by a steep drop in U-Mg (Mg conservation). A dramatic drop of S-Mg neccessitated renewed i.v. infusion of 10 mmol $MgSO_4$ daily over 3 days (Fig. 2; 3). Lastly Mg $OH_2$ mixture was given, 26 mmol Mg daily over 12 days (Fig 2; 4).

On the 11th day both S-Mg and U-Mg rose steeply above the respective target ranges. At the same time the patient became drowsy. The medication was terminated and a rebound parallel fall of S-Mg and U-Mg followed. The fall of the latter below the target range indicated renewed Mg conservation effort (Fig. 2).

Case No. 2. 65 yr old female. Diagnosis, diabetes mellitus + disc prolapse ($L_5,S_1$) + severe kyphosis. Initial S-Mg is 0.679 mmol/l. Oral treatment with Mg $OH_2$ mixture is tried for 44 days, 18 mmol Mg daily. S-Mg does not reach the target range, nor achieve a steady state, but falls to 0.732 mmol/l i.e. exactly the lower border of the reference value (Fig. 3). There was no clinical improvement, which posed two questions: was the dose too low, or the time of medication too short. Experience has shown that with a higher "loading dose" a steady state may be achieved sooner, nevertheless, in cases of severe depletion this takes a very long time, even with higher doses.

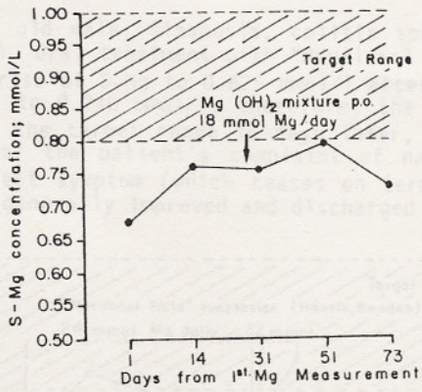


Fig. 3. Case No. 2, treatment trial with $Mg(OH)_2$ mixture.

Case No. 3. 60 yr old man. Diagnosis, Korsakoff's syndrome following delirium tremens with epileptic seizures. Initial S-Mg value 0.500 mmol/l. Treatment with $Mg(OH)_2$ mixture 30 mmol/Mg daily over 35 days achieves a steady state concentration of 0.760 mmol/l, beginning two weeks after the commencement of the treatment. The steady state value is below the target range, but within the reference value (Fig. 4). The simultaneous intellectual recovery of the patient was verified by psychological tests; which showed average values on I.Q. test, yet on memory tests somewhat below the average. On 35th day of treatment the patient was sufficiently clinically recovered to be discharged.

Case No. 4. 54 yr old man. Diagnosis: dementia alcoholica. The initial S-Mg was 0.740 mmol/l i.e. close to the lower border of the reference value. Following treatment with Mg $(OH)_2$ mixture, 64 mmol Mg daily over one week, a steady state at 0.905 mmol/l was achieved (Fig. 4). Clinically, at the same time, there was a gradual clearing of sensorium which allowed the patient to begin regular work within the hospital, which improved his quality of life. It is of great interest that in this case, on reexamination 5 years later, S-Mg was 0.875 mmol/l, i.e. virtually the same as that found 5 yrs earlier. This demonstrates that once a steady state concentration is achieved, it will be maintained over time, provided that there is no alcohol, drug, nicotine abuse, disease or malnutrition occuring in the meantime, to drain anew the body Mg stores. In the interim 5 yrs, the patient was receiving a hospital diet containing 10-20 mmol food Mg daily.

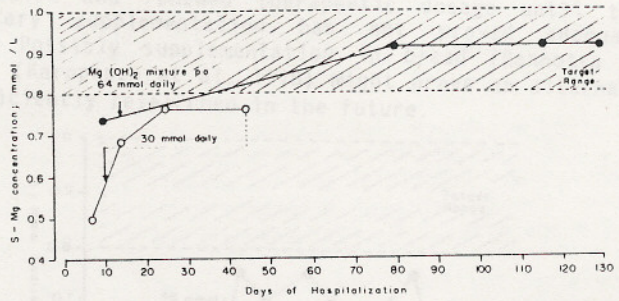


Fig. 4. Case nos 3 and 4, treatment with $Mg(OH)_2$ mixture.

Case No. 5. 24 yr old male. Diagnosis, colitis spastica + sigmoiditis. Initial S-Mg is 0.700 mmol/l. Oral treatment with "Novalucol Forte" suspension, 24 mmol Mg daily was given. A rise of S-Mg to 0.825 mmol/l after 25 days, is followed 49 days later by a new fall to 0.740 mmol/l, therefore, the dose is raised to 32 mmol Mg daily. S-Mg reaches the target range 16 days later, but the medication has to be terminated because of the patient's complaint of nausea. Clinically, except for the latter side effect symptom (which ceases on termination of treatment on 90th day) the patient is generally improved and discharged to commence work (Fig. 5.)

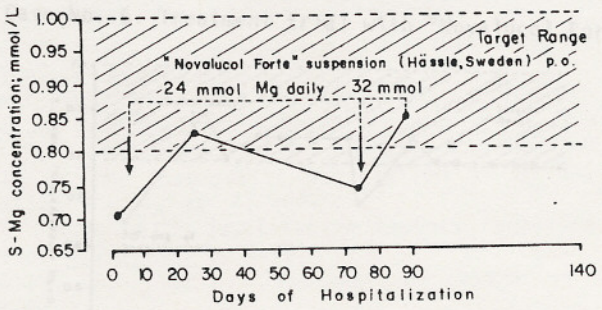


Fig. 5. Case No. 5. Treatment trial with "Novalucol Forte" suspension.

Case No. 6. 55 yr old male. Diagnosis: chronic alcoholism + status post cerebral haemorrhage + liver cirrhosis + chronic pancreatitis + diabetes mellitus. Initial S-Mg is low; 0.445 mmol/l. "Novalucol Forte" suspension, 48 mmol Mg daily was given. After two weeks, S-Mg was 0.650 mmol/l only and clinically, the patient had not improved. The same dose in Case No. 7 was effective after one week (Fig. 7). The response seen in Case No. 6 is typical of very depleted patients, where it can take months to achieve steady state concentration.

Case No. 7. 42 yr old male. Diagnosis, chronic alcoholism and chronic bronchitis. Initial S-Mg is 0.650 mmol/l. "Novalucol Forte" suspension, 48 mmol Mg daily was given. A steady state concentration at 0.850 mmol/l was achieved after a week. Following home leave over the weekend (on 22nd day of hospitalization) and concomitant alcohol ingestion, there was a new fall and a fluctuating S-Mg during a week. A steady state was reached again a week later at 0.800 mmol/l. (Fig. 7). The patient felt improved and requested discharge, which was granted. This case shows how precarious the steady state may prove in the face of a sudden increased loss (here, Mg diuresis due to alcohol ingestion) or increased demand. It also shows that in order to sustain the steady state, a Mg supplement is desirable as suggested by Marier (1982), Durlach (1988) and others. In addition, any viral infection, trauma, disease, physiological and psychological stress will require

renewed revision and renewed therapeutic dosage until the patient stabilizes again. Dietary supplementation has not proved adequate in the author's experience. Possibly supplementation in bread (Ranhotra et al, 1980) or in a mineral salt (Karppanen et al, 1978) might prove an alternative, provided that it will be sufficiently researched in the future.

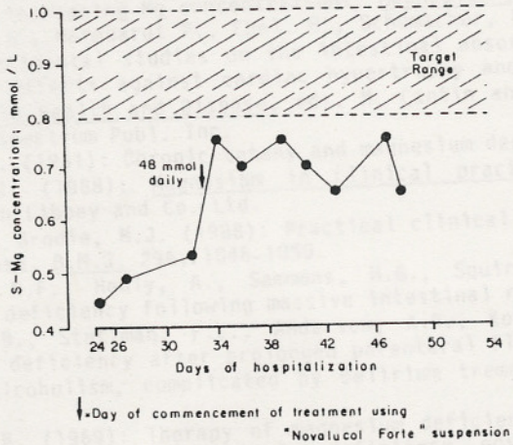


Fig. 6. Case No. 6. Treatment trial with "Novalucol Forte" suspension.

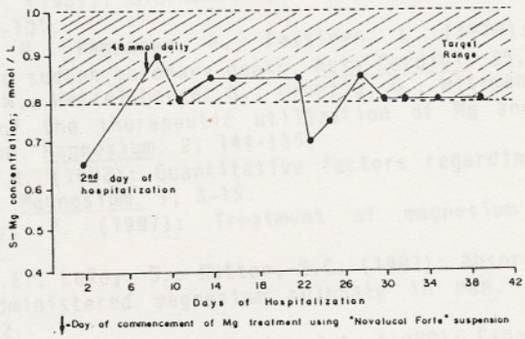


Fig. 7, Case No. 7. Treatment trial with "Novalucol Forte" suspension.

The conclusions drawn from the various treatment trials can be summarized as follows: Clinical improvement appears to coincide with the achievement of a steady state of S-Mg within the target range. The dose and duration of treatment required is proportional to the degree of Mg depletion present. A maintenance treatment may be needed to safeguard a steady state.

SUMMARY:

1) Pharmacological concepts which may serve as guidelines in the therapy are discussed.
2) Target range concentrations for S-Mg and U-Mg are proposed.
3) Examples of therapeutic trails by the trial and error method are presented. These show the importance of ensuring that a steady state concentration within the target range is achieved, and that the dose and duration of treatment required is proportional to the degree of Mg depletion present. To maintain the steady state, a maintenance treatment may be required.

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