Methodological Aspects of Research on the Therapeutic Effects of Magnesium

4th Interamerican Congress of Clinical Pharmacology and Therapeutics Mexico City, Sept. 18–22nd 1990

H. G. Classen, S. Nowitzki, H. F. Schimatschek

Zusammenfassung

Da ein Zusammenhang zwischen Mg-Konzentration und (patho-)physiologischen Effekten besteht, muß der aktuelle Versorgungszustand vor einer Mg-Therapie diagnostiziert werden, die entweder dazu dient, ein Defizit auszugleichen, oder calciumantagonistische Wirkungen erhöhter Spiegel ausnutzt. Die Konzentration des Serum-/Plasma-Mg gestattet die Beurteilung der enteralen Resorption, der Knochenvorräte und renaler Verluste. Unter optimierten Bedingungen betragen die Spiegel 0,75–0,95 mmol/l anstatt 0,70–1,10 mmol/l, wie sie von der Gesellschaft für Magnesiumforschung im Jahr 1986 publiziert wurden. Folglich finden sich Hypomagnesiämien recht häufig bei Patienten mit funktionellen Beschwerden.

Wenn die klinische Wirksamkeit einer Mg-Therapie in kontrollierten Studien geprüft werden soll, entweder im Vergleich zu Plazebo oder zur Standardtherapie, müssen spezielle Probleme beachtet werden, da Mg außerdem ein Lebensmittelinhaltsstoff ist; zusätzlich müssen spezifische Wirkungen der Anionen berücksichtigt werden.

Summary

Assuming a relation between magnesium (Mg) concentrations and (patho-)physiological effects, an exact diagnosis of the actual status should precede Mg therapy, which can either be initiated to compensate a deficit or can make use of pharmacological, calcium-antagonistic effects of increased Mg levels. Serum/plasma Mg concentrations reflect enteral absorption, the reserve of bone stores, and urinary losses. If sampling and serum preparation are optimized, normal levels range between 0.75 and 0.95 mmol/l instead of 0.70–1.10 mmol/l published by the Society for Magnesium Research in 1986. As a consequence, hypomagnesemia occurs rather frequently in patients with functional disorders.

When the clinical efficacy of a Mg therapy shall be ascertained in controlled studies, in comparison to placebo or to a standard therapy, specific problems have to be considered since Mg is also a nutrient and since anionic effects must not be neglected.

Résumé

Si l'on présume l'existence d'une relation entre les concentrations de magnésium (Mg) et certains effets physio(patho)logiques, il convient de poser un diagnostic précis de l'état du patient avant d'entrependre un traitement par le Mg, visant à compenser un déficit ou à utiliser les effets pharmacologiques d'antagonisme calcique d'une hypermagnésémie. Les concentrations sériques et/ou plasmatiques en magnésium traduisent la résorption entérale, les réserves osseuses et les pertes urinaires de cet élément. Si les méthodes de prélèvement et de traitement des échantillons sériques sont optimales, les concentrations normales doivent se situer entre 0.75 et 0.95 mmol/l plutôt qu'entre 0,70 et 1,10 mmol/l (valeurs publiées en 1986 par la Société pour la Recherche sur le Magnésium). Par consequént, uno hypomagnesésémie suvient assez fréquemment chez les patients présentant des troubles fonctionnels.

Lors de l'étude de l'efficacité clinique d'un traitement par le Mg au cours d'essais contrôlés contre placebo ou contre produit de référence, il y a lieu de prendre en considération certains problémes particuliers, puisque le Mg est également un nutriment et qu'il ne faut pas négliger les effets anioniques spécifiques.

1. Introduction

It is generally accepted that an exact diagnosis should precede therapeutic measures, and also that only remedies with proven clinical efficacy, safety and clear-cut indications are to be prescribed, if necessary.

Institute of Biological Chemistry and Nutrition, Department: Pharmacology and Toxicology of Nutrition.

Like other essential minerals — e. g., calcium (Ca), potassium (K) or sodium (Na) — magnesium (Mg) is primarily supplied via food and drinkingwater. Nutritional supply is supposed to be adequate in the absence of any symptoms indicating deficiency or excess, and when input and output are well-balanced. If, on the other hand, clinical symptoms are present and biochemical parameters indicate a disturbed balance, either a deficit or an excess can be supposed [5]. In cases of Mg excess it is indicated to reduce the supply and/or to increase consumption and excretion. If, on the other hand, natural sources cannot be used (e. g., during parenteral nutrition or prolonged vomiting) or if their electrolyte content is too low to maintain physiological body levels, suitable salts can either be administered parenterally as aqueous solutions or orally as supplements. In this con-

text it should be stressed that — in contrast to Ca, K and Na — it is hardly possible to increase easily absorbable dietary Mg levels significantly above the usual content without simultaneously increasing the supply of energy, which is usually undesirable under Western life-style conditions (fig. 1).

Assuming a concentration — effect — curve, three sections are of special interest: Stages of deficiency and excess should be characterized by clinical symptoms and altered biochemical parameters, whereas the absence of symptoms, and biochemical parameters within the normal range should indicate that supply, consumption and excretion are in equilibrium.

In other words, adverse reactions should appear at unphysiological and disappear at physiological levels, respectively.

Concerning Mg, things are however more complex. It is well documentated that Mg is involved in various basic cell functions as well as in the metabolism of other electrolytes, especially in the metabolism of K, Na and Ca [1, 7, 12, 15, 29, 32, 33, 40, 42, 47, see also *Günther,* p. 47]. Due to these various interrelations quite a number of organ and cell functions, enzyme activities and body levels of other electrolytes may, but need not necessarily reflect a deficit or an excess of Mg, since these alterations may also be caused by other specific processes involved in their regulation. For example, typical subjective and objective tetanic symptoms and even severe convulsions may be caused either by a primary Mg deficit or by the primarily impaired metabolism of Ca. Similarly, painful calf cramps or increased sensitivity to digitalis may be either due to a primary deficit of Mg or to a disturbed metabolism of Ca, K and/or Na. Case reports of familial primary hypomagnesemia in infants may demonstrate the complex situation [12, 40]:

Within the first month(s) of life, these infants develop increasing irritability, twitching and severe convulsions which are finally lethal, as can be concluded from family case histories. Biochemically, these patients exhibit pronounced hypocalcemia. Plasma-phosphate levels are frequently increased, but can also be normal or subnormal. In skeletal muscles, K levels were decreased and the Na content was elevated. In all cases reported so far, clinical symptoms persisted or even worsened on the i.v. or oral administration of Ca, together with parathormone, AT 10, vitamin D and/or anticonvulsant therapy. Therapeutic results were only obtained when pronounced hypomagnesemia was recognized and corrected. It should be noted that Mg therapy not only corrected clinical symptoms and hypomagnesemia, but also hypocalcemia, and hyperphosphoremia if present. On temporary discontinuation of the Mg therapy all symptoms gradually developed again.

From these dramatic case reports we learn

a) that clinical symptoms — resembling other electrolyte disorders — may be caused by a primary Mg deficit. Symptoms and secondary electrolyte alterations disappear when physiological Mg levels are restored by specific measures.

Furthermore, we must keep in mind that Mg also exhibits pharmacological activities which can be summarized as

b) calcium-antagonistic activity on systemic administration (fig. 2), resp. following enteral absorption [5, 12, 14, 42],
c) antacidic and laxative activity within the gastrointestinal tract following oral supply and depending largely on the anion [36]
d) and systemic effects due to the respective anion [36]

In order to be able to differentiate between therapeutic effects either due to the compensation of a Mg deficit or to pharmacological effects, it must first be settled what ist „normal", respectively „physiological". Then, the efficacy of Mg must be differentiated against unspecific placebo effects (tab. 1).

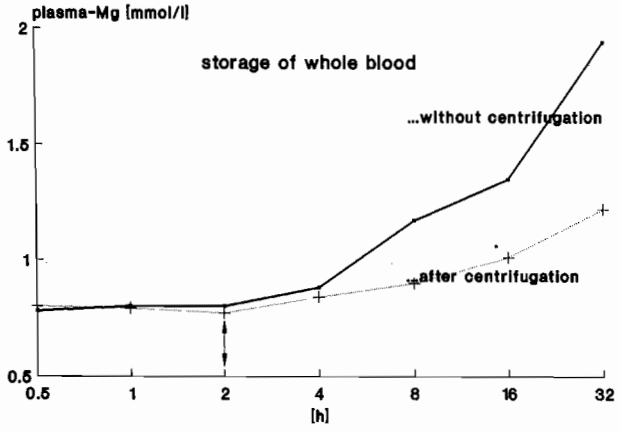

Fig. 1: Correlation between magnesium and energy content of 55 food items. In general, Mg-rich products (nuts, soybeans, sunflowers, whole meal cereals) are also rich in energy.

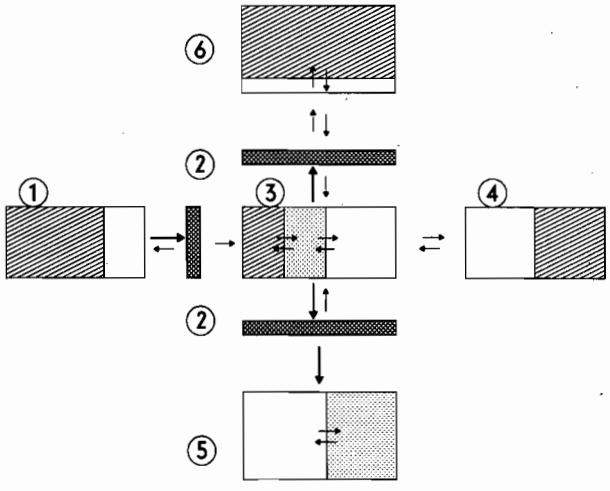

Fig. 2: Electrically stimulated isolated rat ileum: Spasmolytic effects of Mg are reversed by adding equimolar amounts of Ca, thus demonstrating Ca: Mg antagonism.

Tab. 1: Therapeutic Effects of Magnesium.

1. Compensation
• of a magnesium deficit
• of secondary electrolyte alterations (K, Na, Ca, acid-base metabolism)
• of electrolyte-related symptoms
2. Pharmacological effects of increased Mg supply on:
• chymous: increased water content; pH-effects
• membranes: Ca-antagonism, sealing of membranes, release of prostacyclin
• bone: increase of exchangeable pool
urine; effects on Ca: Mg ratio; pH
• intracellular effects (?)
• specific effects of the resp. anion
3. Placebo effects

2. Diagnostic significance of serum/plasma Mg levels

Similarly to Ca, K and Na, quite a number of parameters have been proposed to quantify the actual Mg status (tab. 2). This great variety of procedures already indicates that any of them is fully reliable, or applicable under clinical conditions.

Under practical conditions, the determination of plasma/serum Mg and the relation of the levels obtained to clinical symptoms has gained most attention. — However, there is a marked discrepancy between clinicians and basic research workers.

Under experimental conditions serum Mg is an excellent indicator of body Mg. This is not surprising since — as depicted in fig. 3 — plasma levels represent the central compartment, respectively the vehicle for the transport of Mg from the gut (or other places of invasion) to deeper compartments (cells, cerebrospinal fluid, bone stores) and finally to the kidneys, representing the organ of excretion [7, 26, 28].

Under steady-state conditions plasma Mg levels are in close equilibrium with the exchangeable bone pools — which can act as a buffer of high capacity (+ 35 % to – 60 % of normal) at increased or decreased Mg supply [2, 3, 4, 6, 19, 23, 28, 31] — and with the amounts of Mg excreted via the kidneys [26, 28]. Under controlled and constant dietary supply, analysis of regression revealed a highly significant relation between increasing Mg contents of the diet and the serum Mg levels, which on the other hand, significantly correlated with bone and urinary Mg levels, as shown in tab. 3.

Tab. 2: Quantification of the actual Mg-status [1, 7, 12, 29, 40].

1. Magnesium determinations in biological material
a) non-invasive
urine, saliva, lacrimal fluid, nails, hair
b) invasive
fluids: plasma, serum, whole blood, liquor
cells: erythrocytes, mononuclear cells, epithelia
tissues: biopsies
bone: biopsies
2. Balance studies
Input-output balance
(steady state conditions)
Loading tests, retention
Isotope studies
3. Amounts of Mg needed for the relief of symptoms

Tab. 3: Correlation between plasma/serum Mg levels and the Mg content of various tissues, resp. fluids, of rats kept on diets with different Mg levels. Marked hypomagnesemia (up to – 85 % of controls) was present in Mg deficiency [2, 3, 4, 23, 28, 31]. Note that the coefficient of correlation depends on dietary Mg levels, time of feeding, age and number of animals

Tissue	Coefficient of correlation
Bone (rib, femur, pelvis, cranium)	0.5 to 0.95
Urine	0.6 to 0.90
Erythrocytes	n.s. to 0.3
Cardiac muscle	n.s. to 0.4
Skeletal muscle	n.s. to 0.3
Aortic tissue	n.s. to 0.2
Liver	n.s. to 0.2
Brain	n.s.

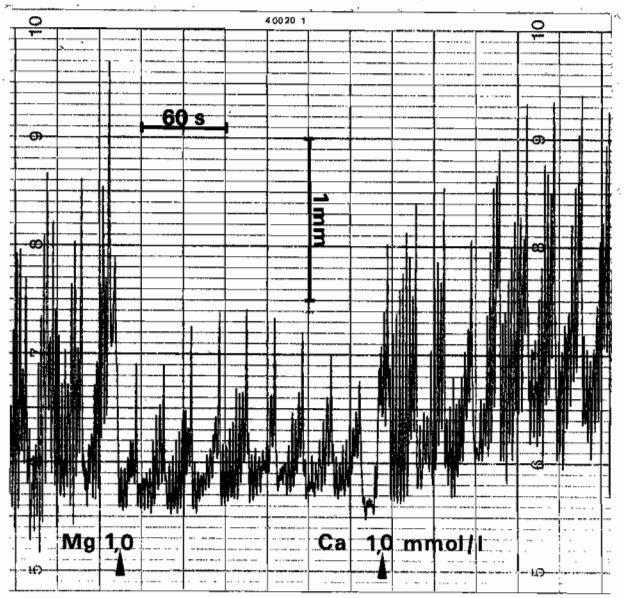

Fig. 3: Schematic presentation of different Mg pools and their interrelation:

1. Gut	30 % of the Mg present in the chymous are absorbable
2. Biological membranes involved in transport	
3. Plasma-Mg:	30 % protein-bound Mg
	30 % ultrafiltrable, complexed Mg
	40 % free Mg^{2+}
4. Bone-Mg:	45 % exchangeable Mg
	55 % apatite-bound Mg
5. Urine-Mg:	partly complexed, partly free Mg^{2+}
6. Intracellular Mg:	90 % bound to ATP, DNA, RNA
	10 % free Mg^{2+}

Serum, respectively extracellular Mg, also closely correlates with pharmacological, mostly Ca-antagonistic Mg effects (fig. 2). — On the other hand, intracellular and cerebrospinal fluid Mg pools do not directly communicate with serum Mg [20] since transmembranaceous and intracellular binding processes regulate uptake and release of Mg, respectively (fig. 3). Hence diverse tissue levels only revealed weak, if any correlation with serum Mg at pronounced Mg deficiency (tab. 3). Therefore, it cannot be expected to detect decreased

total Mg concentrations of a poorly perfused organ (with decreased ATP-levels and decreased bound Mg) by measuring serum Mg! Under such conditions the intracellular Mg content — e.g. of erythrocytes or mononuclear cells — should provide a better correlation, provided that ATP-loss (in the chosen example) occurs simultaneously in all body cells.

With these data in mind one should expect that serum Mg levels are also of substantial clinical significance. The conclusions drawn by clinicians are, however, very contradictory. For example, *Croker* et al. [9] and *Kafka* et al. [21] do not recommend to screen stationary patients for hypomagnese occurred in only ca. 4 % of all cases. In contrast to this, *Durlach* [12], *Dyckner* [13], *Gottlieb* [16] and *Whang* et al. [46] have detected hypomagnesemia in 18 to 46 % of all cases, and Ryzen et al. [34, 35] conclude: „Magnesium deficiency is a common (up to 65 %) clinical finding, which can result in hypocalcemia, hypokalemia, cardiac arrhythmias, muscular weakness and increased neuromuscular excitability". How can these contradictary conclusions be explained?

Most important in this respect is the definition of what is called the „normal range" or the „reference range", reflecting the sum of all biological and systemic errors. The technique of blood sampling and the time elapsing until the preparation and separation of plasma/serum is extremely im blood-sampling, as shown in fig. 4.

It is doubted whether this is always guarenteed in studies where, for example, „healthy blood donators" are used as a reference population! In single cases, breakfast- and lunch-time may also increase the time eplasing until serum or plasma are finally prepared. In addition, the technique and precision of measuring Mg may contribute to the systemic error, although to a lesser extent. — Biological variance increases when hypo- and hypermagnesemic subjects are involved, for example again, when using blood donators who are usually not checked for clinial signs of tetany, or when „apparently healthy patients" are selected in a hospital. Serum protein (albumin) levels should also be controlled. They must be within normal ranges, since hypoalbuminemia can mimic hypomagnesemia [29, 42] due to a decrease of the pharmacologically inactive protein-bound fraction (see fig. 3). In addition, dietary habits [11] including alcohol consumption are frequently disregarded as well as circadian effects and the influences of sex, age, and race.

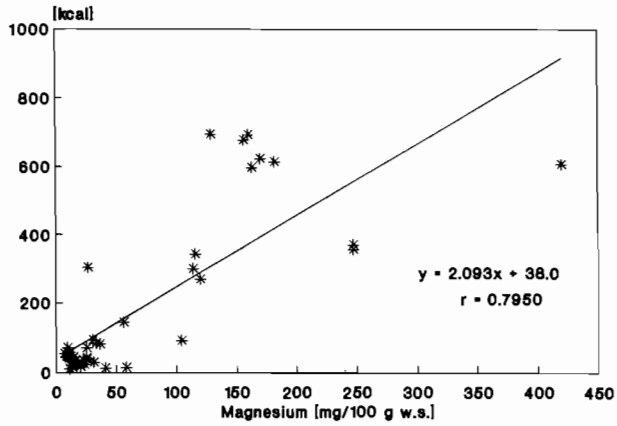

Fig. 4: Contamination of plasma/serum Mg by erythrocyte-Mg as a function of storage-time.

Systemic investigations of *Danielson* et al. [10], *Durlach* [12], *Gueux* et al. [18] and *Lasserre* [24] have consistently shown that serum Mg exhibits normal Gaussian distribution in man. Hence, the normal range may be determined by the arithmetic means, minus, respectively plus twice the standard deviation [30]. In tab. 4 reference values reported in the literature are summarized.

Two facts become quite abvious:

a) to ca. 0.85 mmol Mg/l, and
b) that the relative standard deviation ranges from 15.3 % to 5.7 %!

Correspondingly, the normal range ($\bar{x} \pm 2$ SD) ranges from a maximum of 0.59 to 1.11 mmol/l to a minimum of 0.75 to 0.95 mmol Mg/l!

Tab. 4: Serum (plasma) Mg of healthy persons: Arithmetic means ($\bar{x}$) and standard deviations (SD) in % of $\bar{x}$.

$\bar{x}$	St. Dev. (% of $\bar{x}$)	Sex	Age	N	Comments	Reference
0.78	15.3	f	60–79	19	random telephone method	(45)
0.86	12.4	m	60–79	15	"	(45)
0.85	<15.0	m, f	—	—	no sex effect	(1)
0.86	11.0	f	45–59	26	random tel. method	(45)
0.91	8.6	m	45–59	18	"	(45)
0.85	8.5	f	15–49	4912	AAS	(43)
0.82	8.3	f	15–49	2630	contraceptives	(43)
0.84	7.4	f	15–49	6838	no contracept.	(43)
0.79	7.6	f	36±8	384	normal distribution, AAS	(18)
0.81	7.4	m	38±10	587	standardized	(18)
0.94	7.4	m	—	214	black-coloured miners	(44)
0.82	7.3	f	15–85	50	normal distribution	(10)
0.91	7.3	m	25–44	23	Salt Lake City	(45)
0.88	6.8	m, f	—	50	no tetanics	(12)
0.83	6.0	m	15–85	60	Uppsala, AAS	(10)
0.88	5.7	m, f	48±12	434	normal distribution	(24)

Data collected by Lowenstein and Stanton [25] clearly demonstrate effects of age and sex (tab. 5). It is questionable whether these effects are „physiological" or rather reflect disturbed Mg balance at increasing age and under the influence of female sex hormones. Anyway it should be noted that mean serum Mg levels again average to 0.86 mmol/l, and that the mean percentual standard deviation amounts to 7.6 %, corresponding to an average normal range of 0.73 to 0.99 mmol Mg/l.

Taking all data presented so far into account we are convinced that the normal range of serum Mg from 0.70 to 1.10 settled by our Society in 1986 [5] ist by far too broad. It must be narrowed down, at least to 0.75 to 0.95 mmol/l. Further studies concerning sex and age effects are needed — however it must be guaranteed that the percentual standard deviation does not exceed 6 %!

Tab. 5: Serum-Mg of white-coloured US-Americans, 1971–1974 according to [25].

Age (Y)	Sex	N	mean	SD (%)	Lower level of normal range (mmol/l)
1	m	98	0.90	6.7	0.78
	f	78	0.91	7.1	0.78
2	m	126	0.89	6.2	0.78
	f	121	0.90	6.7	0.78
3	m	167	0.89	7.3	0.76
	f	150	0.89	8.9	0.73
4–5	m	436	0.88	7.4	0.74
	f	428	0.87	6.9	0.75
6–11	m	764	0.87	7.5	0.74
	f	763	0.86	6.4	0.75
12–17	m	886	0.85	6.5	0.74
	f	796	0.84	7.2	0.72
18–24	m	626	0.85	7.6	0.72
	f	1164	0.83	7.9	0.70
25–34	m	672	0.86	7.0	0.74
	f	1539	0.83	7.8	0.70
35–44	m	569	0.86	7.6	0.73
	f	1302	0.84	7.8	0.71
45–54	m	628	0.86	8.7	0.72
	f	705	0.84	8.3	0.70
55–64	m	505	0.86	8.2	0.72
	f	551	0.85	8.2	0.71
65–74	m	1344	0.85	8.2	0.71
	f	1496	0.86	9.4	0.70
mean			0.86	7.6	0.734

3. Documentation of the clinical efficary of magnesium therapy

It functional or organic disorders are supposed to be favourably influenced by Mg [5, 15, 27, 37], Mg therapy may be started either to correct a preexisting deficit (serum Mg < 0.76 mmol/l) [8, 42] or to make use of pharmacological effects of Mg (>0.75 mmol Mg/l) (see Introduction) [41].

Dose-response-effects have been repeatedly described in the literature [3, 4, 14, 23, 31, 44, see also fig. 5]; hence following up single cases includes the monitoring and correlation of objective parameters (see tab. 2) and the relief of symptoms.

Statistically significant proof of the clinical efficacy of Mg can however only be given in comparison to placebo, i.e. an inert substance given in lieu of the active drug, or in comparison to a standard therapy. The efficacy of parenteral Mg therapy, e.g. of acute myocardial infarction, is usually compared to isotonic solutions either of glucose or of NaCl [41], although it may be questioned whether these ingredients are really inert. In the case of high-dosed oral Mg therapy specific problems may arise apart from other well-known biometrical questions concerning inclusion and exclusion criteria of patients, their number, randomization, compliance, time of treatment, a. s. o.

According to the Declaration of Helsinki, informed (written) consent must be given by each patient supposed to participate; this includes an intensive introduction into the metabolism and dietary supply of Mg. Since the patient is primarily interested in the relief of his symptoms and hence is propably afraid to receive placebo, he will certainly think over his dietary habits. He might switch over to Mg-rich food and drinking-water, he might avoid Mg-wasting stimulants and even purchase mineral drinks or supplements in a drugstore. In fact, mean serum Mg levels normalized within 3 weeks when children with hypomagnesemic functional disorders received placebo [8]! Hence — apart from ethical reservations — it is not recommended to use placebo within ambulant supplementation studies.

Alternatively, „standard therapy" can be used for comparison. As discussed in the Introduction, Mg deficiency is frequently associated with secondary electrolyte disturbances. Hence, theoretically, hypomagnesemic hypocalcemia could be treated either with Mg

Serum-Mg mmol/l (log)	Symptoms	Diagnosis
16.60	Cardiac arrest	Hyper
5.60	Respiratory paralysis	
3.60	Inhibition of neuromuscul. transm.	
2.60	Depression of CNS	
0.95	Ca-antagonism	
0.75	Normomagnesemia	Normo
0.45	Latent symptoms Second. electrol. disturb.	Hypo
0.20	Acute symptoms (CNS)	
	Cramps Exitus	

Fig. 5: Serum-Mg (logarithmic scale) and (patho-)physiological. resp. pharmacological effects.

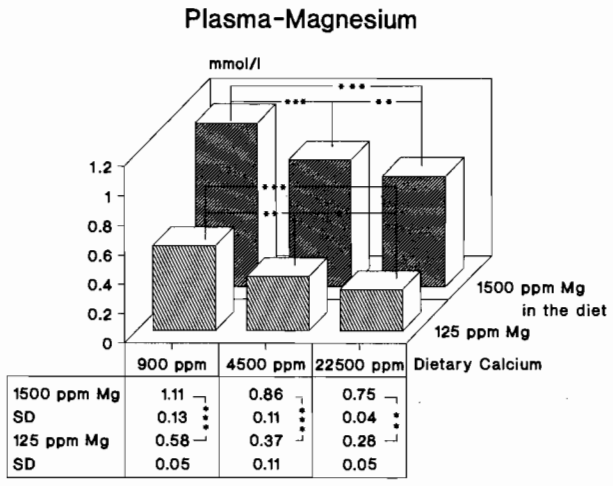

Fig. 6: The effect of increased dietary Ca-levels (900 to 22, 500 ppm) on plasma-Mg in rats kept on low (125 ppm Mg) and „normal" (1500 ppm Mg) magnesium. Ca and Mg were offered as the aspartate-hydrochloride [17, 22].

or with Ca supplements. However, didn't symptoms of infants with familial hypomagnesemia worsen on Ca supplements [40]? In fact, rat experiments revealed a significant tendency towards hypomagnesemia on exposure to high Ca-levels in their diet [17, 22], as shown in fig. 6:

In view of these and probably also other interactions between Mg and standard therapies, one can argue, supposing that Mg therapy can be shown to be superiors,

a) that standard therapy (in this case Ca) was dosed too high — and that „Ca-induced hypomagnesemia" was compared to Mg therapy, or
b) that standard therapy (again Ca) was dosed too low for the proper correction of hypocalcemia (however without affecting Mg balance).

In addition, unspecific local effects on the gastrointestinal tract must be taken into consideration. Unless given as chloride-containing compounds [36], both Mg and Ca exhibit antacidic activies — however in contrast to Mg, Ca may evoke the milk-alkali-syndrome at large doses. Furthermore, Mg will induce stool-softening and finally laxative effects, whereas Ca might induce constipation. Who knows whether these local effects do not modulate systemic functional disorders like the tetanic syndrome — without affecting blood — and tissue levels?

Similar interactions must be considered when deficits of K — due to Mg deficiency — are either treated with Mg or with K supplements, since it has been shown — at least in ruminants — that K may inhibit the enteral absorption of Mg [38, 47]. Despite an ideal solution of these problems cannot be offered it seems necessary to consider them before starting controlled experiments. However, one very important-seeming advise can be given when the efficacy of different cations shall be compared, namely to choose always the same anion at equimolar concentrations: Salts of weak organic and anorganic acids have been shown to induce (compensated) metabolic alkalosis following the oral [36], and also intraveneous administration [39]. Since alkalosis induces intracelular shifts of K and consequently hypokalemia [47], and also decreases the ionized fraction of Ca, thus favouring the development of tetanic symptoms, special care must be paid to avoid that acid-base metabolism is affected at all, or even in a non-uniform direction.

4. Conclusion

In clinical practice, biometrical problems concerned with the proof of the efficacy of a therapy should not be overestimated. Subjects studied in controlled trials are frequently selected using very hard criteria, and the doses applied are often rather high in order to documentate efficacy. Furthermore, even significant results at high probability do not guarantee neither efficacy nor inefficacy of a given treatment in a single case. Hence, if a pient reports complaints and exhibits symptoms resembling electrolyte disorders, the practician should keep possible disorders of Mg metabolism in mind which have been extensively documentated. If (properly prepared) serum Mg levels are then found to be less than 0.76 mmol/l, supplementation is justified. Moreover, pharmacological effects of Mg therapy can be used. The amounts of Mg administered depend on the initial levels. In any individual case the therapeutic efficacy should be carefully monitored.

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(Correspondence to: Prof. Dr. *Hans Georg Classen*, Pharmakologie und Toxikologie der Ernährung am Institut für Biologische Chemie und Ernährungswissenschaft, Universität Hohenheim, Postfach 700 562, D-7000 Stuttgart 70/Hohenheim)