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**FOCUS ON MAGNESIUM: MAGNESIUM DEFICIENCY AND CARDIOVASCULAR DISEASE**

**Magnesium-L-Aspartate Hydrochloride: Experimental and Clinical Data**

H. G. Classen

Epidemiological data suggest that plentiful magnesium (Mg) supply decreases the risk of cardiovascular and other stress-related diseases. Magnesium-L-aspartate hydrochloride (MAH) contains equimolar amounts of Mg and chloride and hence does not affect the equilibrium of non-metabolizable acids and bases. MAH is safe, main pharmacological actions are mediated via Mg-ions and their Ca2+-antagonistic activity. MAH does not bind gastric hydrochloric acid and does not interfere with the enteral absorption of iron, potassium and calcium under physiological conditions, nor with the cytostatic activity of cisplatin and cyclosporine. “Low utilizers” of oral supplements need higher than standard doses (15 mmol) of MAH, individual doses must be increased up to 30–40 mmol. MAH has been proven to attenuate stress reactions in experimental animals, livestock and in humans. Beneficial effects are proven under numerous clinical conditions, eg in obstetrics and gynaecology, in pediatry, cardiology, internal medicine and traumatology. Oral therapy can be optimized by observing plasma/serum and urine Mg levels.

**Key words:** acid-base metabolism, kinetics, stress protection, clinical studies, Ca antagonism, compatibility with oral Fe, K, Ca

Hans SELYE (1907–1982) developed the concept of the so-called “pluricausal diseases” resulting from the combined exposure of an organism to conditioning factors (which may be harmless when applied alone) and strong stressors (which may even increase resistance when applied alone). Although this concept hardly fits into molecular biology, it is generally accepted, for example in internal medicine, where risk factors and provocative events are discussed for many diseases, and also in oncology, where the importance of promoting and inhibiting factors sometimes exceeds the role of tumor initiators. In recent years, magnesium (Mg) has gained increasing interest since severe depletion may act as a stressor, moderate deficiency as a conditioning factor for diverse stress reactions and plentiful supply as an effective anti-stress measure [1]. Plasma/serum Mg is a valuable parameter for the evaluation of the actual Mg status: if pseudohypermagnesaemia due to hypoalbuminaemia is excluded, hypomagnesaemia is a proof of Mg deficit. In the year 2000, a group of experts from the German Magnesium Society proposed a reference range for plasma/serum Mg of 0.76 to 1.10 mmol/L and optimal levels of > 0.80 mmol/L [2]. In an unselected German population of 16,000 individuals, hypomagnesaemia (< 0.76 mmol Mg/L) occurred at a frequency of 14.5 % and suboptimal levels (< 0.80 mmol/L) at a frequency of 33.7 %; in female controls and ambulatory outpatients, frequencies were 17.7 % and 38.8 %, respectively [3]. The evaluation of 23 papers on type I and of 22 papers on type II diabetes revealed that only 11 %, resp. 15 % of these patients had optimal Mg levels of > 0.80 mmol/L supposing that hypomagnesaemia represents an additional risk factor within the so-called metabolic syndrome [4]. This assumption is based on the fact that clinical and epidemiological studies have proven that the risk of coronary heart disease increases with decreasing plasma/serum Mg [2, 5].

In view of the high prevalence of Mg deficiency, its pathophysiological significance and the calcium-antagonistic efficacy of magnesium ions [6], it seemed indicated to summarize data on magnesium-L-aspartate hydrochloride (MAH), an intensively studied compound suitable for Mg therapy.

**Product Profile**

Magnesium-L-aspartate-hydrochloride trihydrate (abbreviated hereinafter as MAH), [(C4H6ClNO4)Mg·3H2O] is protected by national and international patents and has a (theoretical) molecular weight of 245.9. The following structure (Fig. 1) of the complex has been proven [7]:

1 mole of MAH contains equimolar amounts of L-aspartate, chloride and Mg, together with 3 moles of H2O; on a percental weight basis, the complex contains 53.7 % L-aspartate, 14.4 % chloride, 9.9 % Mg and 22 % H2O. Due to this favourable composition it can be predicted — and has in fact been proven — that MAH administered orally or parenterally will not affect acid-base metabolism.

MAH is marketed as MagnesioCard® in Germany (since 1977), Switzerland and Portugal, as Emgecard® in Austria, as Trofocard® in Greece, as Magnesit® in South Africa and as Maginex® in the USA.

![Figure 1. Magnesium-L-aspartate hydrochloride trihydrate](image-url)

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* Dedicated to my friends Drs Bela SOLYMOS and Suzanne VARGA, who readily integrated me into their research team within Hans SELYE’s Institute, Université de Montréal, 1968–69.

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Toxicology

Extensive regulatory toxicology tests on MAH have proven a high degree of safety (unpublished data): single dose toxicity following oral administration revealed LD₅₀ doses of 6.8, 6.9 and 4.5 g MAH/kg b.w. in rats, mice and dogs, corresponding to (rounded) 660, 670 and 440 mg Mg²⁺/kg b.w. Following i.v. administration the LD₅₀ was 216 mg MAH/kg b.w., resp. 21 mg Mg/kg b.w. in rats. Mortality was induced by respiratory paralysis due to neuromuscular blockade, as known from other Mg salts. Repeated dose toxicity was studied in rats and dogs: mild reversible diarrhoea, emesis in dogs and reduced gain of body weight represented major side effects. It should be noted that urine-pH did not reveal treatment-related alka-losis and that daily doses exceeding the single dose LD₅₀ were tolerated after the doses were divided into two or more single doses. Reproduction studies were performed on rats kept on a Mg-deficient diet enriched with increasing concentrations of MAH. Under these experimental conditions underdosing of MAH was significantly more foetotoxic than overdosing as indicated by decreased gain of body weight and the Mg and Ca content of the skeleton of the offspring. Studies on thalidomide-sensitive New Zealand rabbits revealed no teratogenic potential in the offspring, produced by caesarian section, at oral daily doses up to 1710 mg MAH/kb.w. No mutagenic potential was detectable in the standardized Ames-test with 5 test strains, with and without metabolic activation, nor in the micronucleus test in mice. In view of the absence of a genotoxic potential of MAH and a lack of carcinogenicity of its components – MgCl₂ [8] and L-aspartate [9] – a carcino-nogenic potential of MAH can be excluded by extrapolation.

Pharmacology

The main pharmacological actions of MAH are mediated by its content of Mg²⁺-ions and their calcium-antagonistic efficacy [6, 10], for example at the level of cerebral, pulmonary or myocardial blood vessels [11, 12]; under in situ conditions, chloride ions associated with Mg exerted a more potent influence on arteriolar reactivity to an agonist (Ba²⁺-ions) than Mg associated with other anions [13]. Tissues of the whole gastrointestinal tract are also very sensitive to extracellular Mg concentrations [14]: for example the contraction amplitude of electrically stimulated rat ileum was inhibited by 50 % when extracellular Mg²⁺ was increased from zero to 0.8 mmol Mg, added as MAH (see MAH in pediatry!). Similarly the amplitude of spontaneously contracting rat ileum was significantly attenuated by increasing extracellular Mg²⁺ from zero to 1.0 mmol/L, as shown in Figure 2. Addition of equi-molar amounts of Ca²⁺ restored contractility, thus demonstrating Ca/Mg-antagonism at this tissue. The calcium-antagonistic efficacy of Mg readily explains generally increased tendency towards spasms observed in status of Mg deficiency, and of spasmolytic effects following sufficient supply of MAH. In addition Mg/Ca-antagonism is known at the neuromuscular junction and ganglionic impulse transmission. On the level of the brain, the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor deserves special interest since this receptor is specifically blocked by Mg²⁺ [15].

Kinetics, Availability, Interactions

Pharmacokinetics describe relations between the dose administered and concentrations resulting in the body; concentration-bioeffect relations are also assumed. When 14 groups of young SD-rats were fed a basal Mg-deficient diet (34 ppm Mg) enriched with increasing amounts of Mg as MAH (logarithmic intervals of 0.07) during 26 days, significant cubic func-tions could be established between the dose administered and the resulting Mg concentrations in serum (r = 0.98) and bone (r = 0.99) (p < 0.001) [16]. It should be noted that the dose was increased by a constant factor of 1.175, ie not on a linear scale, and that the increase was steeper at low dietary Mg, indicating improved enteral Mg absorption during dietary Mg deficiency (Fig. 3).

When aqueous Mg solutions were administered orally or intraduodenally to cats or rats, plasma/serum Mg increased dose-dependently, concerning the increase, chloride containing compounds were superior to the aspartate or sulfate, and MgCl₂ was more toxic than MAH [17, 18]. Similarly MgCl₂...
was absorbed more rapidly than MAH in dogs, but produced a significantly greater urinary Ca-excretion [19]. In fact, when acid-base metabolism was studied in rats at high dietary Mg concentrations (20,000 ppm Mg), plasma Mg increased as expected. Interestingly, MgCl₂ induced hyperchloroemic compensated extracellular metabolic acidosis (requiring increased renal alkaline excretion for compensation) in contrast to MAH which did not significantly affect acid-base parameters nor plasma chloride. 13 other Mg salts, not containing chloride, showed a tendency towards compensated extracellular hyperchloremic alkalosis which was most pronounced following the citrate [20]. It is well known that the pH of the extracellular fluid is determined by the concentration and chemical properties of the acids and bases dissolved in it: in general, carbonic acid is regulated by pulmonary ventilation. Metabolizable acids – being absorbed from the diet or arising in intermediary metabolism – are regulated by intermediary metabolism. Non-metabolizable acids and bases are absorbed from the diet: they cannot be disposed of by intermediary metabolism or by pulmonary ventilation and hence must be disposed of by renal mechanisms [21]. The principal inorganic bases contributing to the balance are Na, K, Ca and Mg [22] and the principal non-metabolizable acids are hydrochloric acid, phosphoric acid and sulfuric acid. In plasma, [c], ie the concentration (mmol/L) of non-metabolizable bases, amounts to:

\[
[cNa^+ + cK^+ + 2 \times cCa^{2+} + 2 \times cMg^{2+}] - \[cCl^- + 2 \times cSO_4^{2-} + 1.8 \times cP]
\]

\[140 + 4.5 + (2 \times 2.5) + (2 \times 0.75)] - \[102 + (2 \times 0.9) + (1.8 \times 3.4)] = 41 \text{mmol/L}

The anion gap is covered by proteins and organic metabolizable acids. From these data it can be concluded that the supply of higher amounts of alkali earth and alkali metals tends to alkalinization whereas chloride and o-phosphate favour acidification. As outlined (see section “Product Profile”) MAH contains equimolar amounts of Mg and chloride and accordingly does not significantly affect acid-base balance.

Consistent with the presented animal data, MAH dose-dependently increased plasma Mg in volunteers [23]. When 8 healthy volunteers received daily oral doses of 30 and 45 mmol Mg during 7 days as the oxide or as the MAH, bioavailability (estimated by cumulative urinary Mg excretion) of MAH was better than the availability of MgO (p < 0.001); urine pH was decreased (~0.5) during MAH and increased (+0.5) during MgO administration [24]. Interactions of Mg salts with gastric hydrochloric acid are therapeutically used in antacids. As outlined, MAH does not possess this property due to its chloride content [25]. – Textbooks of pharmacology say that Mg and Fe salts may not be taken simultaneously due to the formation of insoluble Mg-Fe-complexes. However, this contraindication does not hold for MAH. Under in vivo-conditions no interaction occurred between MAH and ferrous gluconate [25]. Correspondingly, no interactions occurred following the simultaneous oral administration of MAH plus ferrous gluconate in experimental animals, volunteers and pregnant women [26]. Hence both salts can be taken simultaneously! – With respect to skin diseases it is noteworthy that MAH impeded the enteral absorption of nickel in rats and improved zinc status [27].

Under experimental conditions only very high amounts of MAH impede the enteral absorption of potassium [28] or calcium [29] to a small degree. From a clinical point of view it is much more important that plasma Ca usually increases after the compensation of hypomagnesaemia with supplements of MAH [see later, 37], probably since Vitamin D metabolism is then improved. – As was expected, synergistic effects on the heart muscle of MAH and synthetic calcium antagonists (eg verapamil) were measured in experimental animals [30]. In cancer patients MAH supplements prevented the development of cisplatin-induced hypomagnesaemia without interfering with the cytostatic activity of cisplatin [31]. In rats cyclosporine-induced toxicity was significantly attenuated when the diet was supplemented with plentiful MAH [32].

High Versus Low “Utilizers” of Mg

Studies on families with children presenting with hypomagnesaemia and functional spastic disorders revealed that their mothers suffered more frequently from dysmenorrhea and nocturnal calf cramps (15.6 and 16.9 %) than controls (6.3 and 3.5 %). Familial case reports also suggest negative hereditary effects on Mg utilization [33, 34] which have been proven also for mice by Henrotte et al. [35, 36]. The underlying mechanisms are probably reduced enteral absorption of Mg and/or increased renal losses. In fact when hypomagnesaemic children were supplemented with 10 mmol of MAH daily their mean plasma Mg levels significantly increased and their symptoms significantly improved in comparison to placebo [37]. However, in a subgroup of 15.2 % of the children, plasma Mg did not normalize despite the supplementation, obviously due to relative underdosing. Fehlinger also reported on patients “who had to be titrated with increasing oral Mg doses until their serum Mg increased” [34]. Recently we observed a young woman with migraine-like headache attacks and hypomagnesaemia. Oral daily doses of 15 mmol MAH were completely ineffective during one month – and simultaneously, neither her plasma Mg increased nor urinary Mg excretion. Only when the oral dose of MAH was doubled to daily 30 mmol MAH, Mg levels in plasma and urine increased as well as plasma Ca, and headache disappeared [38]! Similarly, Widman et al., using Mg(OH)₂, had to increase oral Mg doses up to daily 40 mmol in order to obtain significant effects on blood pressure [39].

These examples clearly demonstrate that standard oral daily doses of 15 mmol Mg may not suffice to normalize the Mg status of “low utilizers”. Such patients can only be diagnosed if their plasma and urinary Mg levels are monitored. The drawback of controlled supplemental studies on symptomatic patients using fixed Mg doses without monitoring their biochemical efficacy is obvious, and the reason for insignificant clinical effects may frequently be simply underdosing of subgroups.

MAH Attenuates Stress Reactions

Already in 1932, Kruse et al. observed that Mg-depleted rodents became increasingly sensitive to stress, especially to noise stress [40]. As already discussed, this effect is certainly due to increased sensitivity of the NMDA-receptor [15]. In 1979, Kraemer et al. studied the efficacy of orally administered MAH in cats [41]. The authors could show that Mg levels increased in serum and brain tissue; simultaneously, electrophysiological parameters revealed tranquilizing effects. These effects have been proven by measuring stress hormone levels and related parameters in rats and volunteers [1, 14, 42–44] and in livestock, eg pigs [42]. These CNS effects together with systemic Ca-antagonistic effects readily explain various stress-protecting effects of MAH, especially in hypomagnesaemic individuals.
FOCUS ON MAGNESIUM: MAGNESIUM DEFICIENCY AND CARDIOVASCULAR DISEASE

MAH in Obstetrics and Gynecology

Eclamptic seizures can be evoked by noise stress. Since Mg deficiency sensitizes and plentiful supply protects against noise stress [40]. Mg is the drug of choice for this indication in the US. Splitting and co-workers were able to demonstrate tocolytic effects of oral and parenteral MAH as well as beneficial effects of MAH supplements on pregnancy outcome under controlled conditions. In addition nocturnal calf cramps could be attenuated [45–47]. Pregnancy conditions for Mg deficiency [48]; further losses occur during lactation [49]. Since no unwanted side effects of oral Mg supplements have been reported, plentiful supply of MAH is recommended under these conditions, and also for the treatment of dysmenorrhoea [50].

MAH in Pediatry

Children frequently present with so-called neurovegetative disorders like stomach-ache, headache, chest complaints, leg cramps and neurasthenia. For example an increased frequency of hypomagnesaemia plus hypercalcaemia was detected in children, hospitalized under the tentative diagnosis of acute appendicitis [51]. Epidemiological studies on a total of 2,481 children revealed hypomagnesaemia at a frequency of 21.9 % in children with functional disorders versus 14.3 % in controls [52]. When hypomagnesaemic children presenting with these complaints were supplemented with daily 10 mmol MAH for three weeks mean plasma Mg and Ca levels significantly increased. Relief of complaints was reported by 80.2 % (pediatricians) respectively 82.9 % (parents/patients), these effects were significantly superior to placebo treatment with a corresponding Ca-salt (p = 0.04, resp. p = 0.006) [37]. These clinical data, corresponding to earlier remarks on “Pharmacology”, deserve more attention by pediatricians. The subgroup of “low utilizers” certainly needs higher oral doses of MAH.

MAH in Cardiology

As discussed (see section “Pharmacology”) hypomagnesaemia potentiates, whereas increased extracellular Mg attenuates vasoconstrictor effects of various transmitters on blood vessels, e.g. coronaries. In addition, Ca-overload and excessive consumption of energy-rich phosphates are facilitated during Mg deficiency and blocked by high extracellular Mg [6]. Correspondingly, the production of myocardial necroses by Mg deficiency plus stress (e.g. injections of catecholamines) was prevented in Mg-deficient experimental animals receiving MAH [53–55]. However, when more complex disease models were used, i.e. when acid-base disturbances occurred in addition, only chloride-containing Mg salts offered cardioprotection [6, 18, 53, 56, 57]. In view of the fact that Mg and K losses frequently occur simultaneously MS Scelig has concluded [56]: “Because patients with congestive heart failure and others receiving diuretic therapy are also prone to chloride loss leading to metabolic alkalosis that also interferes with K repletion, the addition of Mg and chloride supplements in addition to the K seems prudent” [56].

Conclusion

Epidemiological data suggest that Mg deficiency is related with cardiac diseases, hypertension and stroke [2, 5]. In fact Dylken and Wester observed a significant decrease in blood pressure when patients received MAH together with diuretics [58]. However, these data were not confirmed by Cappuccio et al. [59]. These contradictions can be partly explained by the fact that normomagnesemic patients or “low utilizers” were included and underdosing of MAH might have occurred [see 39]. Further clinical studies are needed considering the actual level of knowledge to confirm the conclusion and speculation of Weis et al. [60]: “Thus, the possible therapeutic applications of an orally effective Mg2+ salt such as MAH include established indications in frank hypomagnesemic states. In addition, MAH has a potentially broad range of therapeutic activity as an orally effective Ca2+-like membrane stabilizer and as a physiological cellular Ca2+-antagonist.”

References

FOCUS ON MAGNESIUM: MAGNESIUM DEFICIENCY AND CARDIOVASCULAR DISEASE

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