Effects of magnesium-L-aspartate hydrochloride supplements in pregnant sows

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Zusammenfassung

Verfügbarkeit und Verträglichkeit von Magnesium-L-Aspartat Hydrochlorid (MAH) wurde an 24 trächtigen Sauen (Largewhite, Landred, Duroc, Crossbred) im Vergleich zu 24 trächtigen Kontrolltieren untersucht. Zum Zeitpunkt 0 betrug das Körpergewicht rund 150 kg und der tägliche Futterverbrauch 2,4 kg. MAH in einer Dosierung von 13 mg Mg/kg Körpergewicht wurde einmal täglich dem Futter zugesetzt, und zwar ab Tag 0 bis Tag 4 vor der Verpaarung. Blut wurde in den Trächtigkeitswochen 0 – 4 – 8 – 12 entnommen sowie 4 Tage nach dem Ferkeln. – Die untersuchten Trächtigkeitsparameter wurden nicht negativ durch MAH beeinträchtigt, Durchfälle traten nicht auf. In der MAH-Gruppe betrug die Trächtigkeitsdauer 117 ± 2 Tage, die Wurfgröße 10,3 ± 2,1 Ferkel und das Geburtsgewicht 1,6 kg, in der Kontrollgruppe betrug die Trächtigkeitsdauer 116 ± 3 Tage, die Wurfgröße 10,2 ± 2,2 und das Geburtsgewicht 1,5 kg. Zu den 5 Zeitpunkten betrug das Plasma-Mg (mmol/L) in der MAH-Gruppe: 0,87; 0,71; 0,77; 0,81; 0,90 und bei den Kontrollen: 0,84; 0,62; 0,65; 0,74 und 0,85. Das Vorliegen einer Pseudohypomagnesiämie wurde ausgeschlossen. Es bestand ein Trend zu erhöhten Mg-Gehalten in Geweben von Ferkeln aus der MAH-Gruppe. Hieraus wird gefolgert, dass sich während der Schwangerschaft eine Hypomagnesiämie entwickelt und dass MAH sicher und gut verfügbar bei trächtigen Sauen ist; es zeigt sich eine Tendenz zu günstigeren Geburtsparametern und zur Normalisierung des Plasma-Mg nach Supplementation.

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Summary

Availability and tolerance of magnesium-L-aspartate hydrochloride (MAH) was studied in 24 pregnant sows (largewhite, landred, duroc, and crossbred) in comparison to 24 pregnant controls. At time 0, body weight amounted to (rounded) 150 Kg and daily food consumption to 2.4 Kg. MAH was added once daily to the food at a dose of 13 mg Mg/Kg BW, starting 0 to 4 days before mating. Blood was taken at weeks 0, 4, 8, 12 during gestation and 4 days after parturition. Pregnancy parameters were not adversely affected by MAH, no diarrhoea occurred. In the MAH-group, pregnant period was 117 ± 2 days, litter size 10.3 ± 2.1 and litter weight 1.6 Kg versus 116 ± 3 days of pregnancy, litter size of 10.2 ± 2.2 and litter weight of 1.5 Kg in the control group. At the 5 time-points of blood analysis, plasma Mg (mmol/L) amounted in the MAH-group to 0.87, 0.71, 0.77, 0.81, 0.90 and in the controls to 0.84, 0.62, 0.65, 0.74, 0.85. Pseudohypomagnesemia was excluded. There was a trend to increased Mg tissue concentrations in the MAH-group. These data suggest that hypomagnesemia develops during pregnancy as well as the safety and good availability of MAH in pregnant sows with a tendency towards positive effects on pregnancy outcome and normalization of plasma Mg.

Introduction

In obstetrics intravenous pharmacological magnesium (Mg) therapy is frequently used [5, 11]. The main indication is preeclampsia [10] on the basis of Mg-induced vasodilation [1, 17]. Hypomagnesemia in pregnancy conditions for vasoconstriction which is predisposing for preeclampsia [1]. Several studies found that Mg depletion occurs during pregnancy [8, 12, 17, 22, 26, 27]. *Classen* and *Helbig* concluded that the rate of abortions in early and late pregnancy as well as premature births decreased in pregnant women after the administration of Mg due to the inhibition of uterine contractions [6]. Another possible indication for parenteral Mg is preterm labour. A retrospective epidemiological study showed that antenatal exposure of very low birthweight (less than 1500 g) infants to maternal pharmacological Mg supplementation reduced the incidence of cerebral palsy at the age of 3 years or more. This hypothesis agrees with the reports of a neuroprotective role of Mg [2, 18, 19]. However, a critical and comprehensive review of Mg as tocolytic agent concludes that only prostaglandine inhibitors are effective, and an analysis of randomized placebo-controlled clinical trials concluded that parenteral Mg is not better than placebo [14] even on delaying preterm delivery [5] or in preeclampsia [28]. It seems therefore worthy to study whether Mg exerts beneficial effects on pregnancy parameters under experimental conditions. Another interesting aspect is that hyperglycemia caused anomalies in foetuses. The consumption of a diet rich in total sugar (more than 206 g/day) by low income pregnant adolescents was associated with a significant decrease in birth weight and a threefold increase in the relative risk of delivering an small-for-gestational-age (SGA) infant [16]. *Rattanatayarom* [21] showed that hypomagnesemia is associated with hyperglycemia. Therefore it was also studied whether Mg supplementation affects the level of blood sugar during pregnancy.

Materials and methods

Totally 48 (pure bred 47, cossbred 1) multipara gilts (5.2 ± 2.4 preceeding births, body weight ca. 150 kg) were randomly divided into 2 groups of equal size. All sows were fed the same standard food (2.4 kg per day). They were offered tap water ad libitum containing 0.87 mmol/L Mg and 1.66 mmol/L Ca, measured by analysis. Magnesium was used in the form of magnesium L-aspartate hydrochloride (MAH) at a dose of 20 g per pig per day, equivalent to a dose of 13 mg Mg/kg BW/day during all pregnant periods and 4 days after parturition. Mg was added once daily to the food starting 0 – 4 days before mating until parturition. Blood collections from a jugular vein were done at week 0 (a day before Mg was given), at week 4, week 8, week 12, and 4 days (week 16) after parturition, each time during 10 AM-12 AM. For blood glucose analysis blood was collected in NaF tubes. Plasma was separated within 2 hrs after blood collection and measured within 24 hrs with the Peridochrom glucose GOD-PAP method (enzymatic colorimetric method) from Boehringer. For Mg and Ca measurement, blood was collected in heparinized tubes and separated within 2 hrs. Plasma was preserved at –20°C until analysis with atomic absorption spectrophotometry. On the parturition day, litter size, litter birth weight, stillbirths, mummified foetuses, abnormalities, and sex of piglets were recorded. Plasma protein was measured using standard laboratory methods.

Tab. 1: Formula of feed used in the experiment.

Ingredients (Kg)	Pregnant period	Feeding milk period
Broken rice	840	890
Rice bran	600	480
Rice bran extract	200	0
Soy bean meal	250	215
Soy bean meal extrude	0	265
Fish meal	60	105
Salt	7	7
Dicalcium phosphate	24	27
Shell	10	9
Premix	10	10
Lysine	1.6	3.5
Choline	1.0	1.0
Methionine	0	0.9
Total	2 tons	2 tons

Tab. 2: Number of sows at the beginning and the end of the experiment.

Starting number of pigs	Anestrus	Return anestrus	Infertility	Abortion	Dead after parturition	Final number of pigs
Control n = 24	n = 2 8.3 %	n = 0 0 %	n = 1 4.2 %	n = 2 8.3 %	n = 1 4.2 %	N = 18
MAH-group n = 24	n = 1 4.2 %	n = 1 4.2 %	n = 1 4.2 %	n = 3 12.5 %	n = 0 0 %	N = 18

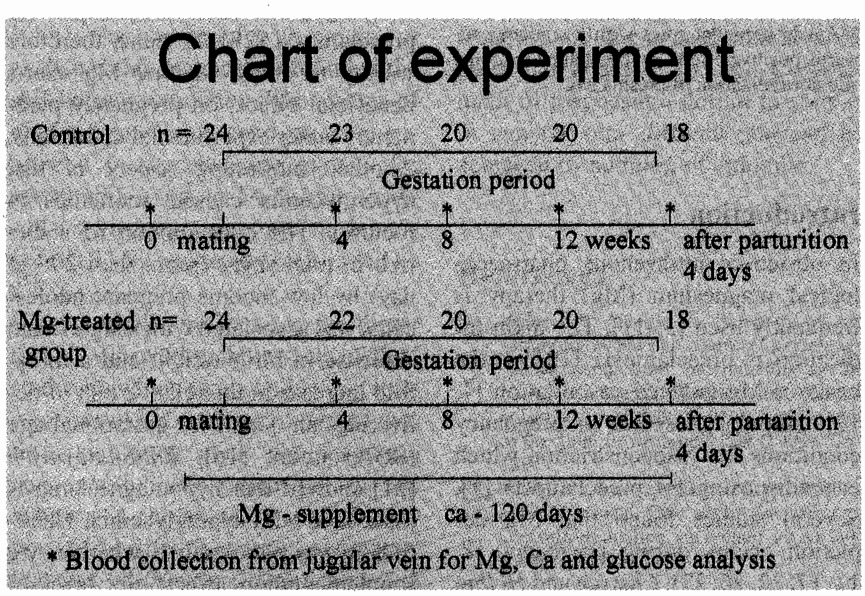

Fig. 1

Statistical analysis

All data were analyzed on statistic computer program SPSS window version 6.1. Data were analyzed for normal distribution (Kolmogorov-Smirnov-test) and homogeneity of variances (Levene's test). For parametric data the t-test for independent samples was applied, (gestation period, litter size, litter birth weight, stillbirths, mummified foetuses, and abnormalities). Plasma glucose was analyzed by one way ANOVA and Scheffe test. For non parametric data Kruskal-Wallis oneway ANOVA was applied, followed by Mann Whitney U-Wilcoxon Rank Sum W-test (plasma Mg, plasma Ca).

Tab. 3: The effect of MAH supplementation on sows and offsprings.

Sows and piglets	Control (n = 18)	MAH-group (n = 18)
Parity	$5^{th} \pm 3$	$5^{th} \pm 2$
Gestation period (days)	116 ± 3	117 ± 2
Litter size (piglets)	10.2 ± 2.2	10.3 ± 2.1
Litter birth weights (Kg)	1.5 ± 0.2	1.6 ± 0.3
Male: female piglets	5 : 5	6 : 4
Total piglets consume	184	186
Stillbirths (%)	5.4 %	4.8%
Mummified foetuses (%)	3.3 %	1.6 %
Abnormality (%)	1.1%	1.1%

Tab. 4: Plasma glucose.

Time of the experiments	Plasma glucose (mg/100 ml) Mean ± SD Control	MAH-group
Beginning (0 weeks)	82.9 ± 7.8^{b} n = 23	81.0 ± 8.8^{b} n = 24
4 weeks gestation	68.7 ± 7.6^{a} n = 23	67.5 ± 9.9^{a} n = 22
8 weeks gestation	68.7 ± 9.3^{a} n = 20	68.8 ± 8.2^{a} n = 20
12 weeks gestation	65.5 ± 8.5^{a} n = 20	66.9 ± 8.3^{a} n = 20
After parturition 4 days (16 weeks)	83.2 ± 10.3^{b} n = 18	89.9 ± 13.6^{b} n = 18

a: significant difference from b: at the same column ($p < 0.01$)

Tab. 5: Total plasma Mg (Mg_m), Corrected plasma Mg (Mg_c) and Total Protein (TP; g/dL) in Controls and MAH treated sows. Plasma Mg was corrected for TP according to [20]:

$$Mg_c = \frac{Mg_m}{0.76 + TP/30}$$

Time	Control			MAH-group		
	Total Mg (mmol/L)	Corrected Mg (mmol/L)	Total Protein (g/dL)	Total Mg (mmol/L)	Corrected Mg (mmol/L)	Total Protein (g/dL)
Week 0	0.84^{b} 0.05 (n = 23)	0.825	7.74 2.05	0.87^{b} 0.09 (n = 23)	0.848	7.97 1.51
Week 4	0.62^{a} 0.10 (n = 22)	0.619	7.24 0.63	$0.71^{a,*}$ 0.08 (n = 21)	0.710	7.20 1.29
Week 8	0.65^{a} 0.05 (n = 19)	0.641	7.63 0.72	$0.77^{a,*}$ 0.17 (n = 21)	0.748	8.09 0.67
Week 12	0.74^{a} 0.07 (n = 19)	0.718	8.13 0.64	$0.81^{a,*}$ 0.08 (n = 20)	0.783	8.25 0.86
Parturition (4 days)	0.85^{b} 0.12 (n = 18)	0.825	8.10 1.16	0.90^{b} 0.09 (n = 18)	0.906	6.98 1.05

a: significant difference from b in the same column ($p < 0.01$)
*: significant difference from Control at the same point of time ($p < 0.01$)

Results

The groups sizes of Controls and the MAH-group amounted initially to 24 gilts and was finally reduced to 2 x 18 animals. Tab. 2 summarizes the reasons.

There were no significant differences between Controls and the MAH-group concerning gestation period, litter size, litter birth weights, stillbirths, mummified foetuses, and abnormalities. Nevertheless, the figures of the Mg-treated group may indicate a tendency towards less stillbirths and mummified foetuses (Tab. 3).

There was no significant difference of plasma glucose between the MAH-treated group and the Controls at all periods of the experiment. Plasma glucose decreased significantly ($p < 0.01$) during gestation in both groups compared to the starting week (week 0). After parturition, plasma glucose increased to the same level as at the beginning (see Tab. 4).

At the beginning and after parturition there were no significant differences of plasma Mg between Controls and the MAH-group. During gestation (week 4, week 8, week 12) the level of plasma Mg decreased significantly at p less than 0.01 in both groups compared with the initial levels of the same group, the lowest level of plasma Mg was observed at week 4. Plasma Mg levels of the MAH-treated groups during gestation (week 4, week 8, week 12) were significantly higher compared and the Controls at p less than 0.01 (see Tab. 5 and Fig. 3). Hence a dose of 20 g MAH/sow/day significantly increased Mg levels in this experiment. Pseudohypomagnesemia was excluded by correcting total measured Mg with the total protein content [20].

Plasma-Ca tended to decrease slightly ($p > 0.05$) in the MAH-treated group compared to the Controls at the same periods of the experiment. Plasma-levels decreased significantly ($p < 0.01$) during gestation, the lowest levels were observed on week 8 (see Tab. 6). Again, pseudohypocalcemia could be excluded.

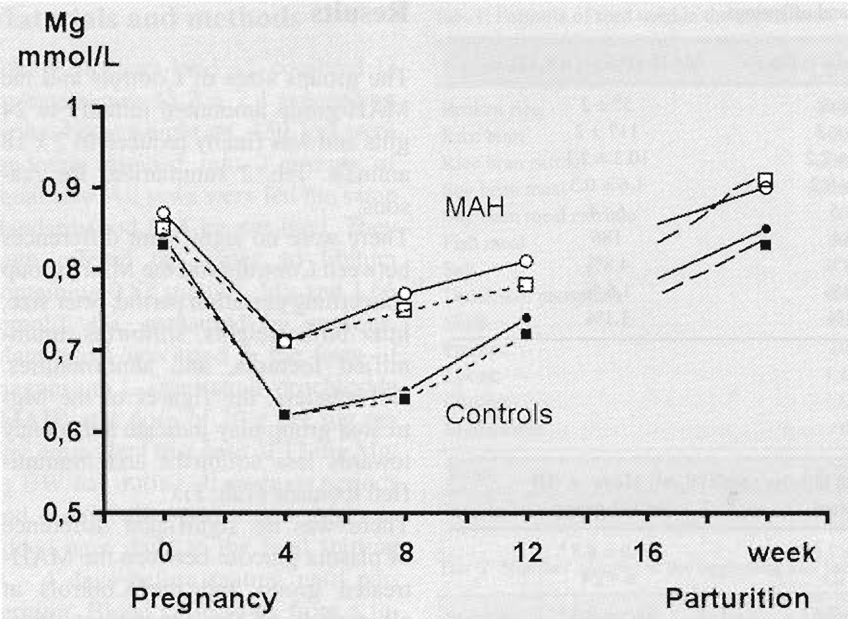

Fig. 2: Plasma Mg levels in Controls and the MAH-group. Data are given for total and corrected (pointed lines) Mg (see Tab. 5)

Levels of Mg and Ca measured in the sows' milk, respectively in the teeth and tails of offsprings are summarized in Tab. 7: There was a slight, but not significant trend towards increased Mg levels in the MAH-group.

Discussion

In human medicine a double blind study has been performed on 568 cases of pregnancy. Mg was orally given at a dose of 15 mmol as the magnesium-L-aspartate hydrochloride. There were significant higher birth weights in the Mg-treated group than in the placebo group, babies of mothers supplemented with Mg showed better Apgar scores, and the results of this study strongly recommend a supplementation of Mg during the whole period of pregnancy [23]. In the present experiments the sample size was much smaller. Nevertheless the figures of litter size, litter birth weight, total piglets and especially stillbirths and mummified foetuses were more favourable in the MAH-group than in the Controls. *Gordon* in 1997 [11] reported that farrowings of long duration and increased time-intervals between piglets at birth are associated with a greater incidence of intrapartal stillbirths, more than 80 % of these stillbirths are believed to occur in the last third of the litter. This might be the reason why in the Mg-treated group less stillbirths occurred. Mg supplementation may improve the duration or decrease time-intervals during parturition.

For plasma glucose no significant Mg effect could be observed. Levels in both groups decreased during pregnancy probably because of the restricted feed energy intake during pregnancy as routine farm management. No pregnant sow developed diabetes during pregnancy [27].

MAH is described as a readily absorbable Mg salt. Magnesium may cause diarrhoea. Thus, only limited amounts can be given by mouth. About 0.37 mmol per kg BW are required to achieve a significant rise in serum Mg levels in rats [7]. In the present experiment, 20 g of MAH per pig per day, equivalent to a Mg dose of 13 mg per kg BW per day or 0.53 mmol per kg BW were orally administered during all pregnant periods and 4 days after parturition. No diarrhoea was

Tab. 6: Total plasma Ca (Ca_m), Corrected plasma Ca (Ca_c)and Total Protein (TP; g/dL) in Controls and MAH treated sows. Plasma Ca was corrected for TP according to [20]:

$$Ca_c = \frac{Ca_m}{0.55 + TP/16}$$

Time	Control			MAH-group		
	Total Ca (mmol/L)	Corrected Ca (mmol/L)	Total Protein (g/dL)	Total Ca (mmol/L)	Corrected Ca (mmol/L)	Total Protein (g/dL)
Week 0	2.80 [a] 0.22 (n = 18)	2.708	7.74 2.05	2.78 [a] 0.20 (n = 21)	2.653	7.97 1.51
Week 4	2.28 [b] 0.15 (n = 21)	2.273	7.24 0.63	2.26 [b] 0.14 (n = 19)	2.260	7.20 1.29
Week 8	2.22 [b] 0.15 (n = 18)	2.162	7.63 0.72	2.17 [b] 0.10 (n = 19)	2.055	8.09 0.67
Week 12	2.48 [b] 0.19 (n = 16)	2.344	8.13 0.64	2.39 [b] 0.13 (n = 17)	2.242	8.25 0.86
Parturition (4 days)	2.46 [b] 0.19 (n = 18)	2.330	8.10 1.16	2.45 [b] 0.13 (n = 18)	2.485	6.98 1.05

[a]: significant difference from [b]: in the same column ($p < 0.01$)

Tab. 7: Mg and Ca concentrations (mmol/L, resp. mmol/kg d.m.) in the sows, milk and in the teeth and tails of offsprings (n = 16-18/group).

	Control		MAH-group	
	Mg	Ca	Mg	Ca
Milk	3.50	20.0	3.58	21.2
	0.63	12.2	0.82	12.0
Teeth	335	6,915	340	6,866
	19	317	32	311
Tails	67.3	643	76.5	620
	26.5	108	36	103

observed during the whole time of observation. Plasma-Mg increased significantly ($p < 0.01$) during weeks 4 to weeks 12 of gestation. However, during gestation Mg decreased significantly ($p < 0.01$) both in the Controls and in the MAH-group compared to the beginning. This effect has been reported in the literature [8, 12, 15, 19, 22, 23]. A similar tendency was observed for Ca [25].

In plasma Mg is bound to proteins, complexed to low molecular weight anions (citrate, phosphate, lactate) or is present in ionized, pharmacologically active form. Depending on the methods applied the percental distribution of the 3 fractions amounts to 28 : 13 : 59 or 26 : 14 : 60 [4]. Several authors have discussed that the decrease of plasma Mg may be primarily a dilutional effect associated with blood volume expansion, indicated by decreased protein concentrations; when corrections were made for increased blood volume and/or altered albumin concentrations normomagnesema resulted instead of hypomagnesemia. Studies of *Handwerker* et al. (1996) however have convincingly demonstrated that true hypomagnesemia, i.e. a decrease also of ionized Mg, occurred in 144 pregnant women [13]; their data are depicted in Fig. 3. The same effect was achieved when in this study total Mg was corrected for decreased proteins according to *Parfitt* et al. [20].

The data of the present experimental study support the findings of *Handwerker* et al. [13], the more since Mg supplements significantly increased Mg levels without changing protein levels.

In conclusion Mg supplements are indicated to correct for hypomagnesemia and are recommended during pregnancy to meet the increased requirement.

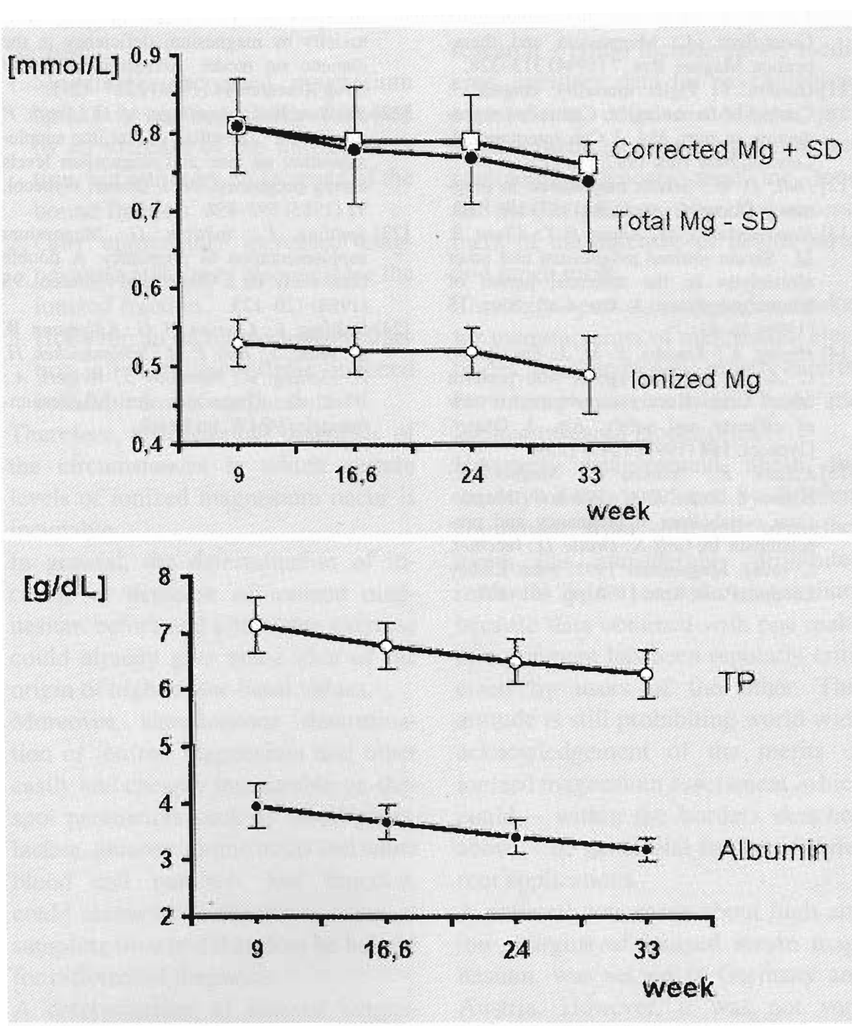

Fig. 3: Mg levels in human pregnancy according to data of *Handwerker* et al. 1996. Total Mg was corrected for total protein according to [20]

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