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# Effects of Peroral Magnesium on Electrolytes and Ventricular Premature Beats in Patients with Cardiac Failure on Diuretic Treatment

## Peroral Magnesium to Patients with Cardiac Failure

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### Zusammenfassung

Fünfundzwanzig herzinsuffiziente, seit über einem Jahr mit Diuretika behandelte Patienten (Durchschnittsalter: 70,0 ± 5,8 Jahre) bekamen 2 Monate lang zusätzliche perorale Gaben von 15 mmol Magnesium-Aspartat-HCl pro Tag. Achtzehn weitere, dieselben Aufnahmekriterien erfüllende Patienten (Durchschnittsalter: 65,3 ± 10,9 Jahre), dienten als Kontrolle. Kalium, Magnesium und Natrium wurden zu Beginn und nach Abschluß der Beobachtungszeit in Skelettmuskeln, Serum und Urin bestimmt. Zu diesen Zeitpunkten wurde außerdem ein 24 Std.-EKG zur Untersuchung ventrikulärer Extrasystolen vorgenommen.

In der behandelten Gruppe nahm die Kaliämie im Gegensatz zu den Kalium- und Magnesiumspiegeln im Skelettmuskel signifikant ($p < 0,02$) zu. Acht Patienten der behandelten Gruppe und ein Patient der Kontrollgruppe kamen für die Bewertung der ventrikulären Extrasystolie in Frage (Grenze > 6,25/Std.). Bei diesen acht mit Magnesium behandelten Patienten wurde die Anzahl der ventrikulären Extrasystolen signifikant ($p > 0,003$) reduziert.

Zusammenfassend läßt sich sagen, daß die perorale Zufuhr von Magnesium bei herzinsuffizienten Patienten unter Langzeit-Diuretikumbehandlung den Kaliumhaushalt verbessern und dadurch die Anzahl der ventrikulären Extrasystolen reduzieren kann.

### Summary

25 patients (mean age 70,0 ± 5,8 years) with cardiac failure, treated with diuretics for more than one year, received additional 15 mmol peroral magnesium aspartate hydrochloride per day for two months. 18 patients (mean age 65,3 ± 10,9 years), fulfilling the same admission criteria, served as controls. When starting and completing the observation period potassium, magnesium and sodium were analysed in skeletal muscle, serum and urine, and 24-hour ECG recordings were performed for analysing of ventricular premature beats (VPBs).

In the treatment group serum potassium increased significantly ($p < 0,02$), but not skeletal muscle potassium or magnesium. 8 of the patients in the treatment group and one in the control group were eligible for evaluation of VPBs (limit > 6,25/hour). In these magnesium treated patients VPBs decreased significantly ($p < 0,003$).

In summary, peroral magnesium supplementation to patients with cardiac failure and on long-term diuretic treatment may improve potassium balance and thereby reduce ventricular premature beats.

### Résumé

Vingt-cinq patients (âge moyen: 70,0 ± 5,8 ans), souffrant d'insuffisance cardiaque et traités par des diurétiques depuis plus d'un an, ont reçu un supplément de 15 mmol/jour de chlorhydro-aspartate de magnésium par voie pérorale pendant 2 mois. Dix-huit autres patients (âge moyen: 65,3 ± 10,9 ans), répondant aux mêmes critères d'inclusion, ont servi de témoins. Le potassium, le magnésium et le sodium ont été dosés dans le muscle squelettique, le sérum et les urines au début et à la fin de la période d'observation et un tracé ECG de 24 heures a été effectué aux mêmes moments afin d'analyser les extrasystoles ventriculaires.

Dans le groupe traité, la kaliémie a augmenté de façon significative ($p < 0,02$), à l'inverse des taux de potassium et de magnésium du muscle squelettique. Huit des patients du groupe traité et un témoin se sont montrés éligible pour l'évaluation de l'extrasystolie ventriculaire (limite: > 6,25/heure). Chez ces 8 patients traités par le magnésium, le nombre des extrasystoles ventriculaires a significativement diminué ($p < 0,003$).

En résumé, une supplémentation magnésique pérorale chez des insuffisants cardiaques sous traitement diurétique au long cours est susceptible d'améliorer l'équilibre potassique et, par conséquent, de réduire le nombre des extrasystoles ventriculaires.


## Introduction

Treatment with thiazides and loop diuretics causes urinary losses of potassium [1] and magnesium [2], which also can be a consequence of cardiac failure in itself [3–5]. The resulting intracellular potassium deficiency and disturbed potassium balance over the cell membrane may lead to potentially dangerous cardiac arrhythmias [6, 7]. Digitalis treatment, which is common in this patient group, may contribute to these hazards [8, 9].

There are different opinions regarding the correlation between the intracellular and serum levels of potassium [10–13]. About magnesium there is agreement on the discrepancy between serum levels and intracellular content [13, 14]. Potassium supplementation alone is ineffective in restoring the intracellular depletion when there is a concomitant magnesium deficiency [15, 16].

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Abbreviations: VPB = ventricular premature beat, FFDS = fat free dry solids.

Magnesium is an essential cofactor for sodium-potassium-ATPase, an enzyme that is engaged in the process maintaining the balance of sodium and potassium over the cell membrane [17]. It has been shown that potassium deficiency during diuretic treatment can be avoided by using potassium-sparing agents, which also have magnesium conserving properties [18–20]. Another way to achieve this goal is by peroral magnesium supplementation [21]. The importance of adequate magnesium levels is demonstrated by the fact that magnesium infusions simultaneously can normalize the cellular potassium content and reduce the frequency of ventricular premature beats (VPBs)[16].

The aim of this study was to investigate the effect of peroral magnesium supplementation during two months on extra- and intracellular potassium and magnesium levels as well as on arrhythmias in patients with cardiac failure on long-term diuretic treatment.

## Material

Assigned to the study were in- and outpatients with cardiac failure and long-term diuretic treatment (more than one year) at the departments of internal medicine of Umeå University Hospital and Skellefteå County Hospital. Potassium supplementation was allowed, but not treatment with potassium-sparing agents. Other exclusion criteria were treatment with drugs containing magnesium, severe renal failure, AV-block II or III, malignant hypertension and recent myocardial infarction or unstable angina. The investigations were performed between October 1983 and April 1988.

Baseline clinical characteristics of 25 patients randomized to receive complementary treatment with magnesium and 18 randomized to the control group are shown in tab. 1.

## Methods

All patients continued their previous treatment during the study. They were randomized either to peroral magnesium supplementation or unchanged treatment as controls. The magnesium supplementation consisted of granulate with magnesium aspartate hydrochloride* 15 mmol/day (360 mg magnesium or 3689 mg magnesium aspartate hydrochloride/day), corresponding to the recommended daily intake [22]. The observation time was two months. On admission and at the end of the study a skeletal muscle biopsy, long-term ECG recording, blood and urine samples were performed. Blood and urine samples were also taken after one month's treatment.

The muscle biopsies and serum and urinary samples were analysed for concentrations of potassium, magnesium and sodium. Urinary 24-hour volumes were recorded. Serum and urine ion concentrations were analysed by conventional autoanalyser technique except for the concentration of magnesium, which was determined by atomic absorption. The method for percutaneous muscle biopsy is described elsewhere [10]. Atomic absorption was used to analyse the ion concentration in the biopsies. Reference values for serum and urine electrolytes are shown in tab. 2 and 3. As normal values for skeletal muscle potassium and magnesium are chosen the results of *Widman* [20], and for sodium the results of *Bergström* [10] (tab. 4).

Long-term ECG was recorded for 24 hours with one channel on the first 26 patients and for 48 hours with two channels on the rest of the patients. The long-term ECG was recorded with portable FM cassette recorders (Oxford) and analysed with the aid of a computer assisted semi-automatic system [23]. All recordings were also controlled manually. The accuracy of the computer-assisted system was evaluated in eight patients with regard to the ability to classify VPBs and non-VPBs. The computer-assisted calcu-

Tab. 1: Clinical characteristics of 25 patients treated with magnesium aspartate hydrochloride and 18 patients in the control group. Figures denote number of patients except where else is mentioned.

| | **Magnesium** n = 25 | **Control** n = 18 |
|---|---|---|
| Men | 9 | 10 |
| Women | 16 | 8 |
| Age (years) (mean ± SD) | 70,0 ± 5,8 | 65,3 ± 10,9 |
| Heart disease | | |
| Ischemic | 19 | 12 |
| Valvular | 2 | 4 |
| Hypertension | 1 | |
| Cardiomyopathy | | 1 |
| Other | 3 | 1 |
| Functional NYHA class | | |
| I | 2 | 1 |
| II | 3 | 4 |
| III | 12 | 13 |
| Not estimated | 8 | |
| Serum creatinine (mmol/l) (mean ± SD) | 97,2 ± 19,0 | 103,6 ± 32,5 |
| Diuretic treatment | | |
| Furosemide | 18 | 18 |
| Bendroflumethiazide | 5 | |
| Bumetanide | 2 | |
| Diuretic treatment time (years) (mean ± SD) | 6,1 ± 4,9 | 4,9 ± 3,5 |
| Not estimated | 9 | 4 |
| Digitalis treatment | 18 | 12 |
| Serum digoxin (nmol/l) (mean ± SD) | 0,90 ± 0,52 | 0,96 ± 0,60 |
| Potassium supplementation | 23 | 15 |
| Potassium dosage (g/day) (mean ± SD) | 2,1 ± 1,8 | 2,3 ± 1,2 |

* Magnesiocard®. Manufacturer: Verla-Pharm, 8132 Tutzing/FRG.

Tab. 2: Serum electrolytes (mmol/l) (mean ± SD) in the magnesium treatment group and in the control group before and after two months. Reference values for Umeå University Hospital.

| | Magnesium group (n = 20*) | | Control group (n = 16*) | | Reference values |
|---|---|---|---|---|---|
| | Before | After | Before | After | |
| | | | $p < 0,03$ | | |
| Potassium | 3,83 ± 0,43 $p < 0,02$ | 4.04 ± 0,39 | 3,91 ± 0,26 | 3,86 ± 0,43 | 3,6 – 4,5 |
| Magnesium | 0,87 ± 0,07 | 0,88 ± 0,09 | 0,89 ± 0,08 | 0,88 ± 0,10 | 0,7 – 1,0 |
| Sodium | 141,7 ± 2,2 | 141,5 ± 3,2 | 141,7 ± 2,4 | 142,6 ± 3,9 | 134 – 148 |

*) Due to missing data, number of analyses for each parameter (treatment/control): potassium 20/14, magnesium 17/13, sodium 20/14.

Tab. 3: Urine electrolytes (mmol/24 hours) (mean ± SD) in the magnesium treatment group and in the control group before and after two monts. Reference values for Umeå University Hospital.

| | Magnesium group (n = 20*) | | Control group (n = 16*) | | Reference values |
|---|---|---|---|---|---|
| | Before | After | Before | After | |
| Potassium | 70,9 ± 36,3 | 75,6 ± 32,8 | 74,2 ± 27,3 | 78,2 ± 25,8 | 50 – 100 |
| Magnesium | 3,03 ± 1,16 $p < 0,01$ | 4,24 ± 1,73 | 3,68 ± 1,12 | 4,67 ± 2 ,58 | 2,5 – 7,5 |
| Sodium | 110,1 ± 56,6 | 116,7 ± 57,9 | 132,3 ± 47,0 | 125,5 ± 50,0 | 50 – 150 |

*) Due to missing data, number of analyses for each parameter (treatment/control): potassium 18/13, magnesium 20/14, sodium 18/13.

Tab. 4: Skeletal muscle electrolytes (mmol/100 g FFDS) (mean ± SD) in the magnesium treatment group and in the control group before and after two months. Normal values for potassium and magnesium according to Widman [20] and for sodium according to Bergström [10].

| | Magnesium group (n = 20*) | | Control group (n = 16 *) | | Normal values |
|---|---|---|---|---|---|
| | Before | After | Before | After | |
| Postassium | 34,9 ± 6,7 | 35,7 ± 5,0 | 35,4 ± 4,1 | 35,8 ± 6,3 | 43,7 ± 3,1 |
| Magnesium | 3,70 ± 0,65 | 3,70 ± 0,49 | 3,91 ± 0,53 | 3,75 ± 0,51 | 4,51 ± 0,40 |
| Sodium | 18,9 ± 8,0 | 16,4 ± 6,9 | 17,8 ± 7,0 | 17,6 ± 5,8 | 11,6 ± 2,7 |

*) Due to missing data, number for analyses for each parameter (treatment/control): potassium 19/16, magnesium 19/16, sodium 19/16.

lated VPB counts were compared with visual counts in two-minute periods randomly selected from each hour during the 24-hour recording. The median sensitivity of detecting VPBs was 100 % in all patients. The median specificity was 100 % (range 97–100 %). In order to confirm a reduction of VPBs with treatment, a minimum of 150 VPBs per 24 hours (6,25 VPBs/hour) in the first recording was chosen [24].

The study was blinded for the persons who analysed the blood, urine and skeletal muscle samples, but not for the physicians or the patients. Of the 34 long-term ECG-recordings analysed, 17 were blinded regarding in which phase of the study they were taken.

The study was given the approval of the local ethics committee.

## Statistics

Student's t-test for paired observations was used to compare the serum, muscle and urine values within the treatment group and the control group. An unpaired t-test was performed to compare the mean changes between the groups. The logarithmic values of numbers of VPBs were analysed with a paired t-test. A p-value of 0,05 or less was regarded as statistically significant.

## Results

Seven of the 43 patients included (five in the treatment group, two in the control group) were withdrawn from the study due to magnesium intolerance in three, beginning of treatment with spironolactone in two, deterioration of cardiac failure in one and bleeding complications at muscle biopsy in one. Twenty patients in the treatment group and 16 in the control group completed the study.

The mean serum electrolytes were all within normal limits before and after the study. Of all serum electrolytes only potassium within the treatment group increased significantly ($p < 0,02$) and compared to the control group ($p < 0,03$) (tab. 2).

Urine magnesium excretion increased significantly during magnesium supplementation ($p < 0,01$) (tab. 3), however not significantly compared to the control group. Potassium excretion increased in both groups, but not significantly.

In skeletal muscle initial values of potassium and magnesium (tab. 4) were below normal limits [20]. In both groups potassium rose slightly but not significantly, and did not reach normal level. There were no significant changes of magnesium and sodium.

In the evaluation of the long-term ECG-recordings, tapes from two of the 36 patients failed for technical reasons. Ten patients were not possible to evaluate because they had atrial fibrillation (six), paroxysmal left bundle branch block (two) or pacemaker rhythm (two). Of the remaining 24 patients, only nine (eight from the treatment group and one from the control group) were eligible for evaluation according to

the criteria used [24]. For details see tab. 5. In this subgroup of magnesium treated patients there was a significant reduction ($p < 0,003$) of VPBs. Among the fifteen patients with less than 6,25 VPBs/hour in the first recording (tab. 6), two in the control group and none in the treatment group increased above this level.

## Discussion

Skeletal muscle potassium and magnesium levels were as expected [5, 20] subnormal from the beginning in the patients with cardiac failure on diuretic treatment. After peroral magnesium supplementation for two months there was a small but not significant increase in skeletal muscle potassium and no change in magnesium. In contrast, *Dyckner* et al. demonstrated a significant increase of these electrolytes after six month's magnesium supplementation [21]. A raise in skeletal muscle potassium has also been found after intravenous magnesium infusion in patients with congestive heart failure [16, 25] as well as in hypomagnesemic patients with short bowel syndrome [26].

It is unclear why muscle potassium and magnesium did not increase significantly after magnesium supplementation in the present study. Absorption of magnesium granulate from the intestine seems to be sufficient according to the results of *Dyckner* et al [21]. Possibly the treatment for two months was too short a time to give the expected electrolyte changes. Another explanation could be an improved compliance of diuretics during the study, which has been suggested in other studies [21], and which can have counteracted the expected effect of peroral magnesium supplementation on potassium balance. Still another explanation could be an insufficient compliance with the magnesium granulate. A small number of patients in the treatment group reported some initial diarrhoea but only three patients were withdrawn. On the other hand, urinary magnesium excretion increased significantly in the treatment group, which indicates an adequate magnesium intake. The numerical decrease of muscle sodium in the treatment group may also indicate an improved function of the cellular membrane sodium-potassium-ATPase. *Dyckner* and *Wester* found higher skeletal muscle sodium in patients with congestive heart failure and diuretic treatment than in controls [5].

The most striking finding is the significant increase of serum potassium in the treatment group, which is somewhat surprising in relation to the small changes in muscle electrolytes, and it contrasts to the finding of *Dyckner* et al. [21]. However, in a recent study [27] on ten patients with chronic compensated heart failure receiving diuretics, an additional daily 17 mmol peroral magnesium for six weeks corrected the serum potassium concentration in contrast to potassium supplementation alone. In that study the skeletal muscle electrolytes were not investigated. The treatment time was even shor-

Tab. 5: Long-term ECG registration. VPBs/hour before and after two months. Patients with **more than** 6,25 VPBs/hour at the beginning of the study.

| Magnesium treatment group | | | |
|---|---|---|---|
| | Before | After | Digitalis treatment |
| Female 71 years | 391,66 | 42,04 | Yes |
| Female 77 years | 39,75 | 3,85 | No |
| Female 70 years | 35,04 | 0,42 | No |
| Female 70 years | 24,46 | 47,88 | Yes |
| Female 75 years | 18,79 | 2,42 | Yes |
| Female 67 years | 13,20 | 0,17 | Yes |
| Female 71 years | 8,90 | 0 | No |
| Male 63 years | 6,96 | 1,76 | Yes |
| Control group | | | |
| | Before | After | Digitalis treatment |
| Male 62 years | 28,40 | 11,60 | No |

Tab. 6: Long-term ECG registration. VPBs/hour before and after two months. Patients with **less than** 6,25 VPBs/hour at the beginning of the study.

| Magnesium treatment group | | | |
|---|---|---|---|
| | Before | After | Digitalis treatment |
| Male 56 years | 0,08 | 0,96 | Yes |
| Male 57 years | 0,15 | 0,06 | No |
| Female 63 years | 0,15 | 0,10 | Yes |
| Female 69 years | 0,19 | 5,38 | No |
| Female 63 years | 0,33 | 0,21 | Yes |
| Female 73 years | 1,54 | 0,66 | Yes |
| Male 75 years | 2,10 | 1,96 | Yes |
| Control group | | | |
| | Before | After | Digitalis treatment |
| Female 57 years | 0 | 0,04 | No |
| Male 51 years | 0,04 | 0,13 | Yes |
| Male 71 years | 0,60 | 0,50 | No |
| Female 78 years | 0,83 | 0,13 | Yes |
| Male 67 years | 0,96 | 106,75 | Yes |
| Female 59 years | 1,13 | 2,21 | Yes |
| Female 57 years | 1,58 | 0,83 | Yes |
| Male 55 years | 5,83 | 10,17 | No |

ter than in our study, which would imply that two months may be enough for a change in serum electrolyte balance.

The increased serum potassium in the present study is probably not explained by decreased urinary excretion or decreased skeletal muscle content. There is a possibility of an altered exchange with other potassium poles, and one might be an increased absorption of potassium from the intestine. There is evidence that sodium-potassium-ATPase is engaged in this absorption process [28], and the magnesium deficiency might influence the enzyme function at this site. Most of the patients in the present study had potassium supplementation, which as far as known was unchanged during the observation time.

Skeletal muscle magnesium was lower compared to the study of *Dyckner* et al [21], which might be explained by differences in diuretic treatment. In that study most of the patients received thiazides, whereas in our study the majority were treated with loop diuretics. Since renal reabsorption of filtered magnesium is about ten times greater in the loop of *Henles* than in the distal part of the convoluted tubules [9] were thiazides act, loop diuretics might cause a more profound magnesium depletion.

Cardiac failure is usually associated with increased VPBs [29, 30], due to structural and hemodynamic factors, hormonal regulating mechanisms, electrolyte disturbances and drug treatment [9]. A remarkable large number of patients in the present study had too few VPBs in the first recording to make it possible to measure a true reduction [24]. The reason for the low frequencey of VPBs could be that many of the patients actually hand only mild to moderate heart failure. Most of the patients in our clinics with severe chronic heart failure are in general treated with potassium-sparing diuretics [31], and consequently these patients were excluded from the present study. Only eight of the patients in the treatment group and one in the control group could be evaluated regarding reduction of VPBs. Although the evaluated patients in the treatment group showed a significant reduction, this must be interpreted carefully because of the small number of patients, and the possibility of regression towards the mean of VPBs observed.

Digitalis toxicity has the same influence as magnesium deficiency on the sodium-potassium-ATPase in the cell membrane [8, 9]. Fifteen patients on digitalis had their long-term ECG-recordings evaluated. None of these had obvious clinical symptoms of digitalis toxicity or serum digoxin levels above the therapeutic level (> 2,4 nmol/l), so it seems unlikely that the increased VPBs were caused by digitalis treatment.

The treatment and control groups were fairly comparable regarding underlying heart disease, functional NYHA class, type and duration of diuretic treatment and concomitant digitalis treatment. There was a difference in age, which was not significant ($p > 0,07$).

## Conclusion

Despite the limitations in the present study, the results indicate that peroral magnesium supplementation may improve the potassium balance and thereby reduce the ventricular premature beats in patients with cardiac failure on long-term diuretic treatment.

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