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Effect of an Acute ACE-Inhibition on Serum Magnesium in Cardiac Insufficiency?

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Zusammenfassung

In einer Pilotstudie untersuchten wir die Wirksamkeit eines ACE-Hemmers auf Hämodynamik, endokrine Regulierung und Magnesiumprofil bei 8 Patienten mit koronarer Herzkrankheit und schwerer Beeinträchtigung der Linksventrikelfunktion. Die Ergebnisse unserer Untersuchung zeigen keine wesentliche Verbesserung des Magnesiumhaushalts durch pharmakologische Behandlung mit ACE-Hemmern. Um die Dosisabhängigkeit einer solchen Wirkung festzustellen, sind zusätzliche Versuche zur Rolle von ACE-Hemmern bei Herzinsuffizienz und zu deren möglichen Wirkungen auf den Magnesiumstoffwechsel erforderlich.

Summary

In a pilot study we investigated 8 patients suffering from coronary artery disease with severly reduced left ventricular function on the efficacy of an ACE-inhibitor, on hemodynamics, endocrine regulation and magnesium profiles. The results of our investigation show no relevant benefit of pharmacological treatment with ACE-inhibitors on magnesium metabolism. If this is dose dependent, further studies of the role of ACE inhibitors in CI and its effects on magnesium metabilism should be done.

Résumé

Au cours d'une étude pilote, les auteur ont étudié l'efficacité d'un IEC, l'hémodynamique, la régulation endocrinienne et le profil magnésémique chez huit patients souffrant de coronaropathie et présentant une diminution sévère de la fonction ventriculaire gauche. Les résultats de cette étude n'ont mis en évidence aucun bénéfice notable du traitement pharmacologique par les IEC sur le métabolisme du magnésium. Pour déterminer si cet effet est dose-dépendant, il convient d'entreprendre des études complémentaires du rôle des IEC dans le traitement de l'insuffisance cardiaque et de effets sur le métabolisme du magnésium.

Introduction

Cardiac insufficiency (CI) is the clinical consequence of pathophysiological changes in progredient stage of cardiovascular diseases, predominantly represented by coronary artery disease and cardiomyopathy. Magnesium deficiency occurs already in early stage of CI, presumably due to catecholamine-induced intracellular magnesium-depletion and consecutive renal excretion [8]. The effect of renal magnesium-loss is enhanced in progredient and end-stage of CI mainly due to therapeutic use of diuretics. Furthermore, the reduced cardiac output evokes an increase in sympathetic activity leading to redistribution of blood flow with reduced kidney blood supply and consecutive over-activation of the renin-angiotensine-aldosterone-(RAA)-system [2]. Since the RAA-system is regulating fluid and electrolyte balance it appears opportune to explore, whether or not the application of ACE-inhibitors in pharmacological treatment of CI has beneficial effects on magnesium metabolism.

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Patients and methods

We investigated 8 patients suffering from coronary artery disease with severly reduced left ventricular function (ejection fraction < 25 %) in a clinical study on the efficacy of cilazapril, an ACE-inhibitor, on hemodynamics, endocrine regulation and magnesium profile.

Patients

The patients were selected for the study respecting the following exclusion criteria: acute heart failure, arterial hypotension or hypertension, myocardial infarction within the last three months, primary valvular heart disease, hypertrophic cardiomyopathy, diseases of the bronchopulmonary system, clinically significant hepatic, renal, gastrointestinal, neurological or hematological disease, serum creatinine levels > 1.8 mg %, primary hyperaldosteronism, known hypersensitivity to ACE-inhibitors, case record of drug or alcohol abuse, and furthermore drugs with a positive inotropic action, except digitalis; beta-blockers, calcium antagonists and all vasodilators were not allowed as concomitant medication and had to be discontinued at least 36 hours prior to the trials with cilazapril.

Study design

Cilazapril is a new ACE-inhibitor which is not in common clinical use yet and was therefore tested on especially selected patients. The substance claims to prove efficacy after sin-

gle-dose-therapy. After 14 days of placebo administration therapy was started. Before and 3 hours after medication with 1 mg cilazapril hemodynamics were measured by right sided heart catheterization using the Swan-Ganz-catheter-unit. Patients underwent bicycle stress test in supine position and hemodynamic measurements were taken at rest as baseline value, at peak, i.e. 75 W workload over 3 minutes, and 15 minutes after peak as recovery value. At the same time serum samples for determination of renin, aldosterone, ANP and magnesium were drawn.

Laboratory evaluation

Serum samples were deep frozen and kept at –20 °C until evaluated by atomic absorption spectroscopy for magnesium and assayed, respectively, by radioimmunoassay for renin, aldosterone and ANP.

Statistics

Statistical analysis was performed by using an interactive statistical package from the SAS-programme.

Results

Hemodynamic data (tab. 1)

Heart rate was slightly above the normal range and showed a tendency to amelioration after application of cilazapril, but did not change significantly. Mean arterial pressure was in the normal range. Right atrial pressure and mean pulmonary arterial pressure were elevated corresponding to the extent of CI and did not change significantly before and after medication. Cardiac index was reduced, in comparison of the data before and after trial with cilazapril there was a slight improvement, but no significant difference. All hemodynamic measurements showed the typical pattern of increase at peak of workload and decrease during recovery.

Hormones and magnesium (tab. 2)

All hormone levels were elevated compared to normal values, magnesium levels were below normal range representing the status of severe hypomagnesemia. The comparison of the hormone and magnesium concentrations before and after application of cilazapril revealed a significant increase ($p < 0.03$) of renin and decrease ($p < 0.02$) of aldosterone at rest, whereas no significant changes appeared in ANP and magnesium levels. During exercise test and after recovery, neither hormone nor magnesium values changed significantly comparing the data before and after drug intake. The profile of all measurements showed an increase at peak of workload and decrease during recovery, except aldosterone which increased further during recovery.

Tab. 1: Hemodynamic data measured before, at peak and after bicycle stress test before and after trial with cilazapril. B = baseline, P = peak, R = recovery; HR = heart rate, MAP = mean arterial pressure, RAP = right atrial pressure, PAPm = mean pulmonary arterial pressure, CI = cardiac index.

Hemodynamic Parameter		HR beats/min	MAP mmHg	RAP mmHg	PAPm mmHg	CL l/min/m²
time	trial	mean value ± std. deviation				
B	before	81 ± 5	92 ± 9	14 ± 3	41 ± 6	2.0 ± 0.2
P	cilaza-	121 ± 7	105 ± 8	28 ±5	62 ± 4	3.1 ± 0.3
R	pril	85 ± 6	90 ± 5	14 ± 4	41 ± 5	2.3 ± 0.2
B	after	84 ± 7	91 ± 5	15 ± 4	43 ± 6	2.2 ± 0.2
P	cilaza-	114 ± 6	102 ± 5	28 ± 5	63 ± 4	3.3 ± 0.4
R	pril	86 ± 7	91 ± 4	15 ± 3	44 ± 6	2.2 ± 0.2
Normal range				< 10	< 30	> 2.5

Tab. 2: Hormone and magnesium concentrations measured before, at peak and after bicycle stress test before and after trial with cilazapril. B = baseline, P = peak, R = recovery; ANP = atrial natriuretic peptide, Aldo = aldosterone, Mg = magnesium; *p < 0.03, #p < 0.02.

Laboratory Data		ANP pg/ml	Renin ng/ml	Aldo pg/ml	Mg mmol/l
time	trial	mean value ± std. deviation			
B	before	370 ± 72	9.7 ± 2.8*	587 ± 116#	0.65 ± 0.04
P	cilaza-	606 ± 99	18.9 ± 5.8	553 ± 125	0.68 ± 0.03
R	pril	432 ± 88	12.1 ± 3.2	622 ± 103	0.64 ± 0.04
B	after	417 ± 96	18.3 ± 5.1*	367 ± 96#	0.64 ± 0.03
P	cilaza-	598 ± 126	20.0 ± 5.6	457 ± 127	0.68 ± 0.03
R	pril	368 ± 80	12.6 ± 4.2	566 ± 143	0.65 ± 0.03
Normal range		15–62	< 3	150–300	0.75–1.0

Discussion

General hemodynamic effects of ACE-inhibitors in CI are the reduction of pre- and afterload with consecutive amelioration of cardiac output and the reduction of heart rate. Effects on the hormonal system of the juxtaglomerular glands are the specific inhibition of angiotensine-converting-enzyme resulting in a diminished production of aldosterone. ACE-inhibitors prevent the over-activation of the RAA-system, which is responsible for fluid regulation and electrolyte balance, especially dealing renal tubular turnover of sodium and potassium and, possibly, also of magnesium [1, 4, 7]. Clinical demand to pharmacological

treatment of CI with ACE-inhibitors is therefore the exertion of beneficial effects on hemodynamics, hormone and electrolyte metabolism. Cilazapril claims to exert the mentioned effects after single-dose-therapy starting one hour after application.

In our study this ACE-inhibitor was tested on selected patients with severe CI. The data of the acute ACE-inhibition showed only moderate changes of hemodynamic parameters, endocrine regulation and magnesium profile. Significant differences of results before and after administration of cilazapril occured between renin and aldosterone concentrations at rest. Although the results of our investigation indicated only minor acute changes, there was insight into the typical action profile of this ACE-inhibitor. Based on these data we draw the following conclusions.

Hemodynamic data

Hemodynamic parameters showed slight changes after drug intake of 1 mg cilazapril.

Hormones and magnesium

The results revealed significant differences between baseline values of renin and aldosterone. Thus, the dosage of 1 mg of cilazapril may be appropriate under resting conditions for inhibiting hormonal effects, but there was no prove for efficacy under work load, especially renin was little responding, presumably due to insufficient dosage. This fact was additionally underlined by recovery concentrations of aldosterone after drug intake which was lower than values before drug application, but nevertheless still elevated. Magnesium levels showed a tendency to increase after use of cilazapril, so this matter may lead to the assumption of a beneficial drug effect in connection with relatively reduced aldosterone output. However, the changes in magnesium concentrations were small and since there is still no clear evidence about a major role of aldosterone in renal turnover of magnesium this assumption remains speculative [3, 5, 6].

Referring to the results of our investigation there appears to be no relevant benefit of pharmacological treatment with ACE-inhibitors on magnesium metabolism. If this is dose dependent, remains to be studied. Therefore, the role of ACE-inhibitors in CI and its effects on magnesium metabolism should be further elucidated.

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