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The Effect of Diuretic Therapy on Mononuclear Cell Potassium and Magnesium

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Zusammenfassung

Thiazide oder Schleifendiuretika, kombiniert mit zusätzlichen Kaliumgaben, bilden seit vielen Jahren den Eckpfeiler der Behandlung kongestiver Herzinsuffizienz oder schwacher bis mäßiger Hypertonie. Bekanntlich bewirken diese Präperate (trotz Kaliumzufuhr) eine Hypokaliämie mit den entsprechenden Folgen. Die schwerste davon ist die Entwicklung ventrikulärer Arrythmien [1]. Weniger bekannt sind die Wirkungen dieser Medikamente auf die Magnesiumkonzentrationen sowie die Tatsache, daß die daraus resultierende Hypomagnesiämie in hohem Maße zu einer hartnäckigen Kaliumdepletion und dem Auftreten ventrikulärer Rhythmusstörungen beiträgt [2,3].

Summary

The corner stone of treatment for congestive heart failure or for mild to moderate hypertension has, for many years, been thiazide or loop diuretics with a Potassium supplement. The effect of these drugs in causing hypokalemia (in spite of supplementation with Potassium) is well known with its concomitant effects, the most serious of which is the development of ventricular arrhythmias [1].
The effect of these drugs on Magnesium are less widely known nor is the fact that the resultant hypomagnesemia is an important contributor to refactory Potassium depletion and to ventricular ectopic arrhythmias [2, 3].

Résumé

Depuis de nombreuses années, la pierre angulaire du traitement de l'insuffisance cardiaque congestive ou de l'hypertension artérielle légère à modérée repose sur les dérivés thiazidiques ou diurétiques de l'anse, associés à une supplémentation en potassium. La responsabilité de ces produits dans l'apparition d'une hypokaliémie (en dépit de la supplémentation potassique) est bien connue, de même que ses effets résultants dont le plus sérieux est la survenue de troubles du rythme ventriculaire [1].
Les effets de ces médicaments sur le magnésium sont moins largement connus et on ne sait pas non plus toujours que l'hypomagnésémie résultante contribue de façon importante à la déplétion potassique réfractaire et à la survenue des troubles du rythme ventriculaire [2,3].

In a study of 38 patients with mild to moderate hypertension, it has been shown that there is a good correlation between thiazide therapy, hypokalemia and increased incidence of ventricular ectopic beats [4]. Thus the degree of Magnesium and Potassium loss was found to be directly related to the dosage of hydrochlorothiazide and the period of time over which the drug was taken. In addition, at standing rest before and during treatment with thiazides, the average number of ventricular ectopic beats increased from 0.60 beats/min. to 1.40 beats/min. whereas during 5 minutes of Bruce stage 1 exercise, the average number of ventricular ectopic beats increased from 0.50 to 5.70 beats/min. There was also a close correlation between changes in serum Potassium and Magnesium and the incidence of ventricular ectopic beats.

Dyckner and *Wester* [5] have also shown that there is a good correlation between duration of thiazide therapy and serum and skeletal muscle Potassium and Magnesium levels. In addition these workers have shown that intracellular potassium deficiency could not be corrected by an infusion of potassium but could be corrected by an infusion of magnesium [6].

The status of mononuclear cell Potassium and Magnesium levels in these patients has been less well studied. Although serum levels of these cations do not necessarily mirror intracellular levels [6], there is evidence that mononuclear cell Potassium and Magnesium levels may more accurately reflect skeletal and cardiac muscle concentrations [7, 8]. Since this method has the advantage of being less invasive and more easily repeatable than muscle biopsy, we have performed a number of studies on the effects of various treatments, both in patients with congestive heart failure and in patients with hypertension without heart failure, on serum and mononuclear cell Potassium and Magnesium. The methodolgy has been previously described [9].

A prospective, randomized study was carried out on 155 patients who were

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followed up for 6 months after acute myocardial infarction [10]. Of the 85 patients who were in congestive heart failure, 48 received Furosemide with Potassium supplements and 37 received a combination of Hydrochlorothiazide with Amiloride (Moduretic). The remaining 70 patients did not require diurectis and served as controls. At 6 months, serum levels were unchanged in all groups. However mononuclear Potassium and Magnesium levels were statistically significantly lower in the group receiving Furosemide (tab. 1).

In a retrospective study [11], 45 patients receiving diuretics for from 6–60 months were examined. Thirty one patients were being treated for congestive heart failure and 14 for hypertension without congestive failure. Of the 31 patients with congestive failure, 9 received Furosemide alone, 12 Furosemide with Potassium supplementation and 10 received Moduretic. Of the 14 patients with hypertension, 6 received Chlorothiazide alone and 8 received Moduretic. Serum Potassium was significantly lower than controls (4.25 ± 0.05 and 3.2 ± 0.33 mmol/l respectively; $p < 0.01$) in the patients receiving Chlorothiazide with no difference in the other groups. On the other hand, mononuclear cell Potassium was significantly lower in patients receiving either loop or thiazide diuretics than in either controls or patients receiving Moduretic (tab. 2). In addition, the longer patients had received loop or thiazide diuretics the lower the potassium levels in their mononuclear cells ($r = 0.558$; $p < 0.001$). Mononuclear cell Magnesium levels also tended to be lower in these groups although the difference from controls or patients receiving Moduretic did not reach statistical significance.

Thus it appears clear that treatment with loop or thiazide diuretics, even with Potassium supplementation will result in measureable decreases in intracellular Potassium and Magnesium levels not seen when a Potassium (and Magnesium) sparing diuretic is used.

Tab. 1: Mononuclear cell cation levels in 155 patients with congestive heart failure treated with either furosemide and Potassium or moduretic.

	NO DIURETICS	FUROSEMIDE	MODURETIC
NUMBER OF PATIENTS	70	48	37
	MONONUCLEAR CELL CATIONS (fmol/cell)		
POTASSIUM	37.0 ± 0.8*	25.4 ± 1.4**	40.0 ± 1.6*
MAGNESIUM	5.0 ± 0.1*	1.5 ± 0.2**	4.7 ± 0.2*
CALCIUM	6.0 ± 0.3+	4.3 ± 0.4++	5.6 ± 0.5

*/** $p < 0.001$; +/++ $p < 0.003$
Adapted (with permission) from Arch. Int. Med. (1986) 146:1301.

Tab. 2: Treatment with loop or thiazide diuretics or moduretic in patients with hypertension or congestive heart failure. Effect on Mononuclear cell cations.

MONONUCLEAR CELL	POTASSIUM	MAGNESIUM (fmol/cell)	CALCIUM
CONTROL (n = 50)	36.2 ± 3.0*	4.0 ± 0.2	5.8 ± 0.6
CONGESTIVE HEART FAILURE			
FUROSEMIDE (n = 9)	28.2 ± 1.8**+	3.0 ± 0.6	6.0 ± 1.2
FUROSEMIDE + SLOW K (n = 12)	24.6 ± 1.4*■	3.6 ± 0.6	6.0 ± 1.0
MODURETIC (n = 10)	34.4 ± 1.4+■	4.0 ± 0.8	5.6 ± 1.2
HYPERTENSION			
CHLOROTHIAZIDE (n = 6)	26.2 ± 1.0**	3.4 ± 0.5	6.2 ± 1.2
MODURETIC (n = 8)	38.2 ± 1.4	4.8 ± 0.9	5.6 ± 0.7

*/** $p < 0.001$; ■/■ $p < 0.001$; +/+ $p < 0.01$
Adapted (with permission) from Cardiology (1988) 75:17.

The effects of an ACE inhibitor, Enalapril, were studied in 15 elderly patients (mean age 74, range 67–86 years) in severe refractory congestive heart failure (8 in New York Heart Association class IV, 6 in class III and 1 in class II) [9]. All were receiving optimal therapy with digitalis, diuretics and vasodilators and were either in a steady state for at least 1 week before entry into the trial or deteriorating. 10 patients received 5 mg and out 10 mg of Enalapril daily. During the 12 week follow up period 1 patient died of intracerebral hemorrhage and 2 were lost to follow-up. There was a significant improvement in the functional capacity of the remaining patients (tab. 3) with no significant change in serum creatinine or blood urea nitrogen or in the Potassium or Magnesium levels of mononuclear cells .

Tab. 3: Functional capacity (New York heart Association Classification) of patients before and after treatment with enalapril.

	weeks	before*	2**	6+	12++
class	IV	9	1	1	1
	III	5	8	5	2
	II	1	5	8	9
	I	-	-	-	-

*/** $p < 0.046$; **/+ $p < 0.08$; +/++ $p < 0.32$
*/++ $p < 0.005$
Reproduced (with permission) from Cardiology (1988) 75:338.

There are many reports in the literature regarding the association between Potassium and Magnesium

depletion and increased cardiac risk from arrhytmias [12–18]. Of particular interest is the placebo controlled double blind study of the European Working Party on High Blood Pressure in the Elderly [19]. This study included 840 patients who were over the age of 60 years at entry, who received either placebo or a potassium sparing diuretic for from 1–7 years. There was no decrease in the rate of acute myocardial infarction. However the mortality from acute myocardial infarction was decreased by 60 % in the treated group ($p < 0.043$) and may well reflect the fact that the potassium sparing drug prevented the electrolyte disarray seen with conventional diuretics [20]. It would therefore seem prudent to threat patients who require diuretics with either a Potassium (and Magnesium) sparing drug or with an ACE inhibitor where possible.

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