Interactions between magnesium and drugs in the treatment of hypertension

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Zusammenfassung

Der Herzmuskel kann ungünstig durch eine antihypertensive Medikation beeinflußt werden, die Magnesium (Mg^{2+}) -Verarmung verursacht oder den Influx dieses Ions durch das Sarcolemma reduziert. Die üblichen Diuretika führen zu Hypermagnesiurie, die auch durch den Hemmer von ACE (angiotensin converting enzyme), das Captopril, verursacht werden kann. Einige Calcium-Antagonisten interferieren mit der Mg^{2+}-Aufnahme ins Myocard. Die einmalige Gabe verschiedener Diuretika, eingeschlossen Clopamid 5 mg, Chlorthalidon 100 mg, Hydrochlorothiazid 25 und 50 mg, Xipamid 5, 10 und 20 mg, und Furosemid 40 mg steigert signifikant die Mg^{2+}-Ausscheidung im 24-Stunden-Urin. Die Schleifendiuretika Muzolimin 30 und 40 mg, und Torasemid 5 und 10 mg sowie das kaliumretinierende Diuretikum Amilorid, 5 und 10 mg, haben keinen negativen Effekt auf die Mg^{2+}-Ausscheidung. Die Mechanismen, über die die üblichen Diuretika die Mg^{2+}-Exkretion induzieren, sind komplex und können Parathormon und das Renin-Angiotensin-Aldosteron-System einschließen. Der Betablocker Pindolol, Amilorid und der ACE-Inhibitor Captopril mindern jeweils Mg^{2+}-Verluste über den Harn, die nach akuter Gabe von Diuretika erfolgen, welche am distalen Tubulus angreifen. Einige experimentelle Daten lassen vermuten, daß Mg^{2+}-Mangel an der Pathogenese der essentiellen Hypertonie beteiligt ist. Studien an Hochdruckpatienten stützen diese Annahme aber nicht überzeugend. Mg^{2+}-Mangel kann einen koronaren Risikofaktor beinhalten. Entsprechend sollte eine Verarmung an Mg^{2+} während der Langzeit-Behandlung der arteriellen Hypertension vermieden werden. Das klinische Bild des Mg^{2+}-Mangels ist unspezifisch; der Verdacht sollte aber immer bestehen bei Langzeit-Behandlung mit Mg^{2+}-ausscheidenden Diuretika und insbesondere dann, wenn andere Faktoren vorhanden sind, die die Entwicklung eines Mg^{2+}-Mangels begünstigen.

Summary

The heart may be adversely affected by antihypertensive medications causing magnesium (Mg^{2+}) depletion or reduced inflow of the ion across the sarcolemma. Common diuretics cause hypermagnesiuresis as may the angiotensin converting enzyme (ACE) inhibitor captopril. Some calcium antagonists interfere with Mg^{2+} entry to the myocardium. Single doses of various diuretics including clopamide 5 mg, chlorthalidone 100 mg, hydrochlorothiazide 25, 50 mg, xipamide 5, 10, 20 mg, and furosemide 40 mg significantly increase 24 hour urinary excretion of Mg^{2+}. The loop diuretics muzolimine 30, 40 mg and torasemide 5, 10 mg and the postassium-retaining diuretic amiloride 5, 10 mg do not affect Mg^{2+} excretion adversely. Mechanisms whereby common diuretics induce Mg^{2+} excretion are complex and may involve parathyroid hormone and the renin-angiotensin-aldosterone system. The beta blocker pindolol, amiloride and the ACE-inhibitor captopril all reduce urinary losses of Mg^{2+} which occur in response to acute doses of distal tubular diuretics. Some experimental evidence suggests that Mg^{2+} deficiency might contribute to the pathogenesis of essential hypertension. Studies in hypertensive patients do not provide convincing support for this postulate. Mg^{2+} deficiency may be a coronary risk factor. Accordingly Mg^{2+} depletion should be avoided during prolonged treatment of arterial hypertension. The clinical presentation of Mg^{2+} deficiency is non-specific but the condition should be suspected whenever therapy with magnesiuretics has been prolonged, particularly when other factors favouring the development of Mg^{2+} deficiency are present.

Résumé

Les médicaments antihypertenseurs peuvent avoir un effet préjudiciable sur le cœur en provoquant une déplétion en magnésium (Mg^{++}) ou une diminution de l'influx de l'ion à travers le sarcolemme. Les diurétiques usuels, de même que le captopril, un inhibiteur de l'enzyme de conversion de l'angiotensine, provoquent une hypermagnésiurie. Certains inhibiteurs calciques interfèrent dans la pénétration de Mg^{++} dans le myocarde. Des doses uniques de divers diurétiques — par exemple 5 mg de clopamide, 100 mg de chlortalidone, 25 ou 50 mg d'hydrochlorothiazide, 5, 10 ou 20 mg de xipamide et 40 mg de furosémide — augmentent significativement l'excrétion urinaire de Mg^{++} sur 24 heures. En revanche, 30 ou 40 mg de muzolimine et 5 ou 10 mg de torasémide (diurétiques de l'anse), de même que 5 ou 10 mg d'amiloride, un diurétique d'épargne potassique, n'ont pas d'effet préjudiciable sur l'excrétion de Mg^{++}. Les mécanismes de l'hypermagnésiurie indiuite par les diurétiques courants sont complexes et peuvent impliquer la parathormone et le système rénine-angiotensine-aldostérone. Le pindolol (bêta-bloquant), l'amiloride et le captopril (un inhibiteur de l'enzyme de conversion de l'angiotensine) réduisent tous les fuites urinaires de Mg^{++} induites par les doses aiguës des diurétiques d'effet tubulaire distal. Certaines données expérimentales plaident en faveur d'un rôle du déficit en Mg^{++} dans la pathogénie de l'hypertension essentielle, mais les études menées chez des malades hypertendus n'étayent pas cette hypothèse de façon convaincante. Le déficit en Mg^{++} peut constituer un facteur de risque coronarien. Il faut donc prévenir un déficit en Mg^{++} pendant le traitement au long cours de l'hypertension artérielle. Le tableau clinique du déficit en Mg^{++} n'est pas spécifique, mais un tel déficit doit être suspecté en cas de traitement prolongé par des médicaments magnésiurétiques, surtout s'il existe en même temps d'autres facteurs susceptibles de favoriser le développement d'une carence en magnésium.

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The role of magnesium (Mg^{2+}) in both the healthy and malfunctioning cardiovascular system has recently become the focus of increasing research and interest [8, 20, 28, 29, 30, 39, 73, 79, 85, 86, 94, 96, 98]. The magnesium ion appears necessary for optimal regulation of electrical phenomena at the sarcolemma and also, in certain circumstances, for the maintenance of an appropriately low tone in the coronary arterial musculature. Magnesium deficiency may be complicated by clinically important cardiac arrhythmias and has also been identified as an important risk factor for cardiac ischaemic episodes including myocardial infarction [3, 20, 28, 94]. Most of the adverse cardiovascular effects associated with Mg^{2+} deficiency may be accounted for by the induction of significant intracellular electrolyte imbalances including increases in cytosolic Ca^{2+} and Na^{+} and a decrease in cytosolic K^{+} [3, 39, 64, 95].

The heart may be adversely affected by antihypertensive formulations which promote Mg^{2+} depletion or reduce the inflow of the ion across the sarcolemma and the antihypertensive efficacy of these substances could also be unfavourably affected by deranged Mg^{2+} turnover within vascular tissues. Common antihypertensive diuretics are known to augment urinary Mg^{2+} excretion and may thus alter the balance of the element adversely, particularly if other potential causes of Mg^{2+} deficiency are present [6, 40, 60, 65, 66, 68, 71, 72, 74, 75, 90, 96, 97].

Captopril increases urinary Mg^{2+} output acutely in healthy individuals given single doses (100 mg) of the preparation whereas the newer angiotensin converting-enzyme inhibitors enalapril and perindopril do not share this characteristic ([45, 48] *Reyes, A. J., Leary, W. P.* and *van der Byl, K.*: unpublished). Some Ca^{2+} antagonists may also interfere with Mg^{2+} entry in the myocardium [22, 23].

Effects of diuretics on magnesium turnover

Diuretics and the treatment of hypertension

The diuretics most commonly used at present are divisible into three groups in accordance with their principal sites of action within the kidney. Loop diuretics such as furosemide, muzolimine, piretanide and bumetanide exercise their main renal effect at a common site located in the thick ascending segment of the loop of Henle. Early distal tubular diuretics, including the thiazides, chlorthalidone, clopamide, indapamide and xipamide, act at specific acceptors for each substance in the first portion of the distal convoluted tubule. The K^{+}-retaining diuretics spironolactone, amiloride and triamterene act in the terminal part of the distal convoluted tubule where they inhibit transparietal exchange between Na^{+}, which is normally reabsorbed from the pre-urine, and K^{+} and H^{+} which are excreted from the milieu interieur.

In view of their widespread clinical use, loop and tubular diuretics can be referred to together as common diuretics [65]. The standard diuretic dose of a loop diuretic is that which causes a similar natriuretic response to furosemide 40 mg assuming the drugs are given as single doses to healthy individuals under carefully controlled circumstances [65, 76]. Under similar experimental conditions the standard dose of an early distal tubular diuretic would have comparable effects to hydrochlorothiazide 50 mg [65, 76].

Diuretics in the three main groups are not interchangeable in the management of hypertension [69]. Loop diuretics do not conform to the strict definition of antihypertensive diuretics [76] and should not be used as monotherapy for uncomplicated hypertension; they are useful when hypertension and renal insufficiency coexist, in treatment of hypertensive crises and when the coadministration of Na^{+}-retaining antihypertensives such as vasodilators and some sympathetic blockers has caused a syndrome of pseudo-resistant hypertension [76]. Early distal tubular diuretics are widely employed as drugs of first-choice for the monotherapy of uncomplicated essential hypertension and their use in combination with other antihypertensive substances is also accepted practice in many countries [50, 100]. The K^{+}-retaining diuretics are not used as monotherapy but are sometimes administered with antihypertensive diuretics in order to limit the severity of electrolyte imbalances associated with the prolonged use of these substances.

Diuretics and magnesium depletion

Potassium deficiency secondary to increased urinary losses of the ion has usually been identified as the most important cause of cardiac arrhythmias developing during prolonged therapy with common diuretics [27, 31, 32, 57, 59]. In fact there is no clear relationship between plasma K concentration and the incidence of cardiac arrhythmias during prolonged treatment with diuretics; when appropriate laboratory studies were carried out Mg^{2+} depletion appeared of greater relevance and supplementation of this element suppressed the arrhythmia irrespective of the plasma K^{+} concentration [10, 15, 52, 56,

58, 61, 87, 95, 99]. These findings justify careful evaluation of the role common diuretics play in total Mg^{2+} turnover.

The effects of single doses of various diuretic formulations upon 24-hour urinary outputs of fluid and electrolytes have been studied in healthy biologically equivalent volunteers [67]. Under the strictly controlled conditions applied, all the diuretics used with the exception of torasemide 5 mg induced significant increases in 24-hour urinary outputs of Cl in comparison with placebo and, with the exception of muzolimine and torasemide also increased 24-hour Na^+ excretion (Tab. 1). Torasemide, which has a significant diuretic effect during the first 6 hours after dosing did not increase 24 hour fluid output. Urinary K^+ output was significantly reduced by amiloride 5 and 10 mg and was unaffected by low doses of hydrochlorothiazide (25 mg) or muzolimine (30 mg); standard doses of all common diuretics tested significantly increased 24-hour urinary K^+ excretion. Amiloride had no statistically significant effect upon 24-hour Mg^{2+} output although a weak tendency to retain Mg^{2+} in a dose-dependent manner was detectable. The loop diuretics muzolimine (30, 40 mg) and torasemide (5, 10 mg) had no significant effect on 24-hour urinary Mg^{2+} excretion whereas the other common diuretic formulations, including furosemide 40 mg, hydrochlorothiazide 25 and 50 mg, chlorthalidone 100 mg, clopamide 5 mg and xipamide 5, 10 and 20 mg all increased Mg^{2+} output significantly with respect to placebo. Data from other sources confirm that furosemide 40 mg causes hypermagnesiuresis under similar experimental conditions [26] and prove that the loop diuretic piretanide [84] and the early distal tubular diuretic tienilic acid [5] also increase urinary Mg^{2+} excretion acutely in healthy subjects. Amiloride does not affect Mg^{2+} excretion [26, 42]. Thus, on the basis of actue experiments in healthy individuals, it appears that common diuretics that cause clinically significant natriuresis induce hypermagnesiuresis which might be expected to lead to Mg^{2+} depletion in some individuals subjected to prolonged treatment with these preparations. No data are available on the effects in hypertensives of chronic treatment with diuretics upon total body or myocardial Mg^{2+} content. However several studies have shown that a fall in plasma Mg^{2+} concentration occurs in many patients treated with common diuretics for prolonged periods [15, 18, 99]. Prospective studies, carried out in an area where the diet is frequently deficient in Mg^{2+}, showed that monotherapy of hypertension with different diuretic formulations significantly reduced plasma Mg^{2+} concentration but only after at least 12 weeks treatment [37, 38, 44] (Figs. 1 and 2).

Tab. 1: Percentage changes in mean 24-h urinary outputs of fluid and various electrolytes, after administration of single doses of various diuretic formulations to healthy volunteers, with respect to corresponding mean control 24-h outputs

n	Diuretic Formulation	% urine volume	% Cl^-	% Na^+	% K^+	% Mg^{2+}
13	Amiloride 5 mg	19*	10	39**	−28***	−5
13	Amiloride 10 mg	43****	32***	65****	32***	−7
9	Clopamide 5 mg	25****	83***	85****	25*	27***
9	Chlorthalidone 100 mg	69***	150****	165****	70***	87***
13	Hydrochlorothiazide 25 mg	21****	29****	33****	21	73****
19	Hydrochlorothiazide 50 mg	38****	64****	61****	30*	25*
13	Xipamide 5 mg	20****	39****	47***	41***	28***
13	Xipamide 10 mg	63****	107****	120****	55***	50****
13	Xipamide 20 mg	63****	102****	111****	80****	40****
9	Furosemide 40 mg	50***	49**	48***		51*
10	Muzolimine 30 mg	14***	38****	33***	21	9
10	Muzolimine 40 mg	10	24**	18*	32*	11
14	Torasemide 5 mg	−4	23	28	−2	11
14	Torasemide 10 mg	−6	44*	26	1	2

n = number of cases

Significances of the differences between mean control post-dosing 24-h urinary outputs:

* $p < 0.05$
** $p < 0.02$
*** $p < 0.01$
**** $p < 0.001$

Mechanisms of diuretic induced hypermagnesiuresis

Urinary Mg^{2+} output in man normally ranges from 4 to 8 mmol.day^{-1} (100 – 200 mg.day^{-1}). The manner in which Mg^{2+} is handled by different areas of the nephron is unknown in man and, for lack of suitable evidence, is usually assumed to resemble that in the rat despite the obvious limitations of such an approach. In rats 20 – 30 % of filtered Mg^{2+} is reabsorbed at the proximal convoluted tubule, 50 – 60 % at the thick ascending portion of the loop of Henle, and 1 – 5 % at

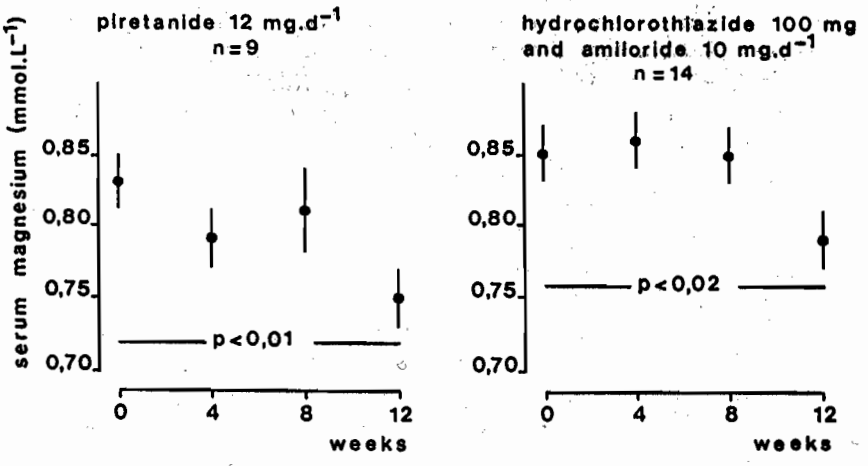

Fig. 1: Changes in serum Mg^{2+} concentration (mean ± S.E.M.) during the treatment of patients suffering from essential hypertension with piretanide 6 mg b.i.d. or with a combination of hydrochlorothiazide 50 mg and amiloride 5 mg b.i.d. n = number of cases. Adapted from [37] *Leary* and *Reyes*, 1981b (left hand panel) and [38] *Leary* and *Reyes*, 1981a (right hand panel), by courtesy of South African Medical Journal

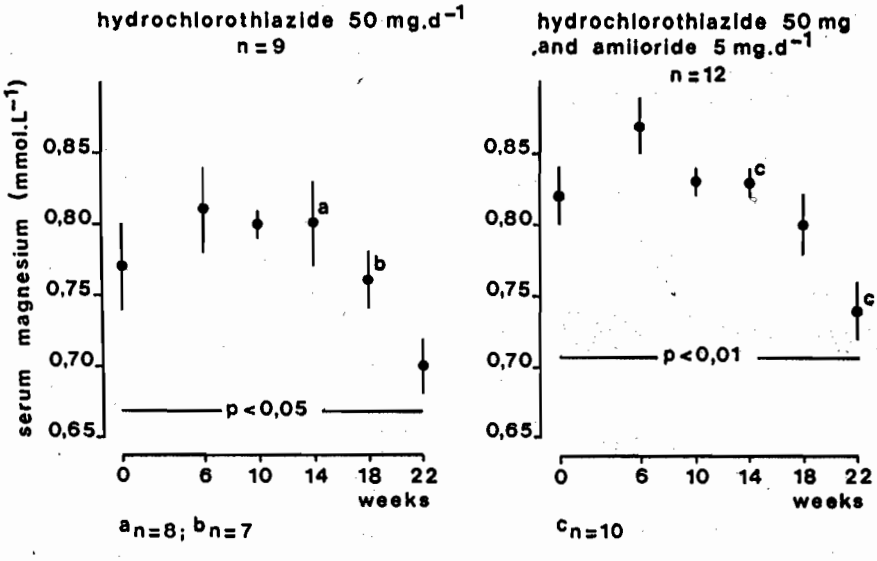

Fig. 2: Changes in serum Mg^{2+} concentration (mean ± S.E.M.) during the random and double blind treatment of patients suffering from essential hypertension with hydrochlorothiazide 50 mg or with a combination of hydrochlorothazide 50 mg and amiloride 5 mg. n = number of cases. Adapted from [44] *Leary* et al., 1984b, courtesy of Magnesium-Bulletin

the distal convoluted tubule [63]. Parathyroid hormone (PTH) enhances reabsorption of the element at the loop of Henle and possibly also at the distal convoluted tubule [54].

Loop diuretics

Loop diuretics block transparietal reabsorption of Mg^{2+} at the thick ascending limb of the loop of Henle; this appears to be independent of the effects loop diuretics exert upon Cl^- and Na^+ at the same site. Loop diuretics increase urinary Ca^{2+} excretion thus diminishing plasma Ca^{2+} and increasing PTH levels [21, 24, 54, 55]. The resultant mobilisation of Ca^{2+} and Mg^{2+} from bone increases the glomerular filtration and ultimate excretion of these cations although the increase in PTH would tend to augment Mg^{2+} reabsorption at the nephron [54]. When Mg^{2+} intake is high and no other cause of Mg^{2+} deficiency is present, loop diuretics are unlikely to cause significant depletion of the ion since intestinal Mg^{2+} absorption tends to increase when plasma concentrations fall [67].

At present no information is available concerning the effects upon serum Mg^{2+} concentrations of chronic therapy with the loop diuretics muzolimine and torasemide. Muzolimine (30,40 mg) and torasemide (5,10 mg) ([47] *Reyes, A.J., Leary, W.P and van der Byl, K.:* unpublished did not increase 24-hour urinary Mg^{2+} output significantly in healthy volunteers (Tab. 1)). This was largely due to marked reductions in urinary Mg^{2+} flows that followed significant increases in excretion of the element immediately after dosing. Thus these preparations, which are of relatively limited use in the treatment of hypertension, stimulate the mechanisms responsible for loop-diuretic-induced increases in urinary Mg^{2+} excretion and have the potential to cause Mg^{2+} depletion in some patients. (Early distal convoluted tubular diuretics). These compounds, which are drugs of first choice as monotherapy for uncomplicated essential hypertension, appear to increase renal Mg^{2+} excretion in a dose-dependent manner (Tab. 1).

It is not clear how distal tubular diuretics increase urinary Mg^{2+} excretion to a significant degree given that only 1 – 5 % of filtered Mg^{2+} is reabsorbed in the distal convoluted tubule, at least in the rat [63]. The fact that amiloride tends to retain Mg^{2+} [54, 83] suggests the possibility that Mg^{2+} might be partially subject to processes similar to those affecting K^+ in the terminal portion of the distal convoluted tub-

ule [12, 13, 14]. This postulate has been tested in a number of carefully monitored experiments carried out upon healthy volunteers.

The effects on urinary electrolyte outputs of single doses of hydrochlorothiazide 50 mg, placebo and a formulation containing hydrochlorothiazide 50 mg and amiloride 5 mg were compared [43]. Whereas both active drugs had significant diuretic and natriuretic actions only hydrochlorothiazide increased 24-hour Mg^{2+} output (Fig. 3). This suggested the possibility that diuretic-induced secondary hyperaldosteronism might promote urinary Mg^{2+} excretion [19, 42, 43]. To further evaluate this question urinary excretions of fluid and electrolytes were measured in healthy individuals who were given single doses of placebo, captopril 100 mg, hydrochlorothiazide 25 mg, and a formulation of captoptil 100 mg and hydrochlorothiazide 25 mg in random order (Fig. 4). Captopril increased urinary Mg^{2+} excretion but reduced hydrochlorothiazide-induced hypermagnesiuresis markedly and increased natriuresis when the two drugs were given together. These results indicate that captopril is a magnesiuretic per se [48] and that it probaly counteracts thiazide-induced Mg^{2+} losses to some extent by reducing plasma aldosterone levels; this finding is consistent with the hypothesis that aldosterone is involved in the control of urinary Mg^{2+} output. Since beta-adrenergic blockade might be expected to blunt renin-mediated increases in aldosterone secretion caused by diuretics, studies were carried out to determine whether beta adrenergic blockade would decrease diuretic-induced hypermagnesiuresis. A combination of sotalol 320 mg and hydrochlorothiazide 50 mg was found to increase urinary Mg^{2+} output acutely to the same extent as a single dose of hydrochlorothiazide 50 mg [46]. This result suggested that beta-adrenergic blockade does not influence thiazide-induced changes in urinary Mg^{2+} output, irrespective of any fluctuations in plasma aldosterone levels which might occur. In a subsequent study single doses of the distal tubular diuretic clopamide 5 mg, the beta-adrenergic blocker pindolol 10 mg and a combination of the two were given to healthy volunteers in random order [80]. Pindolol blocked the magnesiuretic and kaliuretic effects of clopamide (Fig. 5). This result appears to endorse the hypothesis that diuretic-induced Mg^{2+} excretion is partly mediated throught aldosterone and also provides support for the practice of treating hypertension with a regimen including both a beta-adrenergic blocker and a distal tubular diuretic.

In the controlled experiments referred to in Tab. 1 and Fig. 3, 4, and 5 urine was collected at specific intervals after dosing and mean accumulated excretions of solutes as continuous functions of time were fitted by a mathematical model (Fig. 6). The time-derivative of this model gives the mean urinary flow of any solute as a function of time and allows accurate description of the time courses of substances

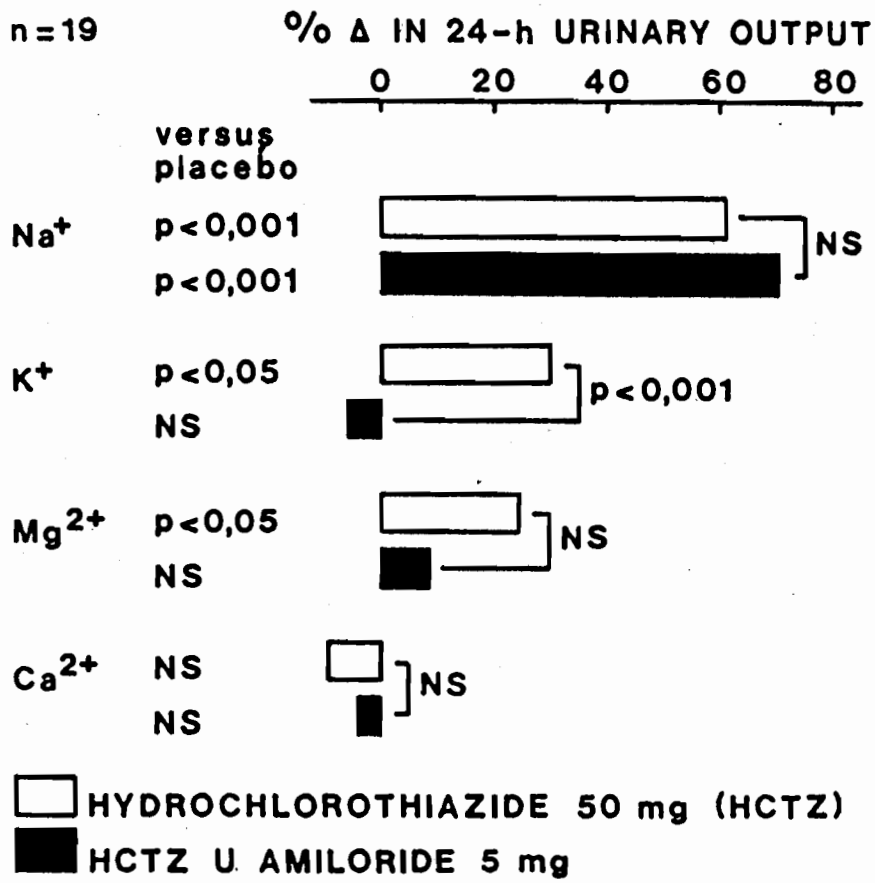

Fig. 3: Summary of the results from a study in which healthy volunteers were given separate single doses of hydrochlorothiazide 50 mg and of a combination of hydrochlorothiazide 50 mg and amiloride 5 mg, double blind and in random order. Bars depict percentage changes in mean 24-hr urinary electrolyte output after these diuretic formulations with respect to mean post-placebo 24-h renal excretions. n = number of cases; NS = non-significant. Adapted from [43] *Leary* et al., 1984a, by courtesy of Current Therapeutic Research

excreted in the urine [70]. This technique has provided further insight into possible mechanisms whereby distal tubular diuretics induce hypermagnesiuresis. When placebo is given to healthy volunteers the mean urinary flows of Na^+ and Mg^{2+} are almost superimposable [77] (Fig. 7). After the administration of a distal tubular diuretic to the same subjects the mean urinary excretions of Na^+ and Mg^{2+} become separated in time; mean Na^+ flow antecedes Mg^{2+} flow by several hours (Fig. 8). This finding indicates that some relatively slow, indirect, mechanism contributes to hypermagnesiuresis caused by distal tubular diuretics. Changes in plasma aldosterone levels might account for this time-lapse, since, when a diuretic is given, plasma aldosterone may peak at approximately the same time as maximal natriuresis. Early distal tubular diuretics decrease urinary Ca^{2+} output [1, 2, 11] thus raising plasma Ca^{2+} and lowering plasma PTH [88]. These changes cause hypermagnesiuresis by decreasing Mg^{2+} reabsorption in the loop of Henle and could partly explain the delay in urinary Mg^{2+} flow with respect to urinary Na^+ flow since the increase in plasma Ca^{2+} and fall in PTH would occur later than maximal natriuresis.

Potassium-retaining diuretics

When a single dose of a combination of amiloride 5 mg and hydrochlorothiazide 50 mg was administered acutely to healthy individuals no significant change in urinary Mg^{2+} output occurred (Fig. 3). However the chronic administration of this combination may result in increased urinary Mg^{2+} losses and hypomagnesaemia in some hypertensives (Fig. 1 and 2), possibly because amiloride, like distal tubular diuretics, decreases urinary Ca^{2+} excretion with resultant hypercalcaemia and a reduction in PTH [1, 11].

Hypermagnesiuresis induced by captopril

A small but statistically significant increase in 24-hour urinary Mg^{2+} output was found when single doses of captopril 100 mg were given to healthy volunteers [46]. The acute administration of a combination of captopril 100 mg and hydrochlorothiazide 25 mg to the same subjects induced a marked increase in 24-hour Mg^{2+} excretion although the increment was significantly less than that induced by hydrochlorothiazide 25 mg and greater than that which occurred after captopril 100 mg when either drug, was given alone [48]. These findings suggest that captopril increases urinary Mg^{2+} output by a direct action on the kidney and conversely, under certain circumstances, may retain Mg^{2+} by decreasing plasma aldosterone levels.

The overall importance of angiotensin-converting-enzyme (ACE) inhibitors in Mg^{2+} homeostasis remains uncertain at present. Acute studies have failed to demonstrate any acute hypermagnesiuretic effect in response to single doses of enalapril [45] or perindopril *[Reyes, A.J., Leary, W.P. and van der Byl, K.:* unpublished*]* and no data is available from controlled prospective studies in which plasma or tissue Mg^{2+} levels have been monitored during prolonged therapy with ACE-inhibitors, common

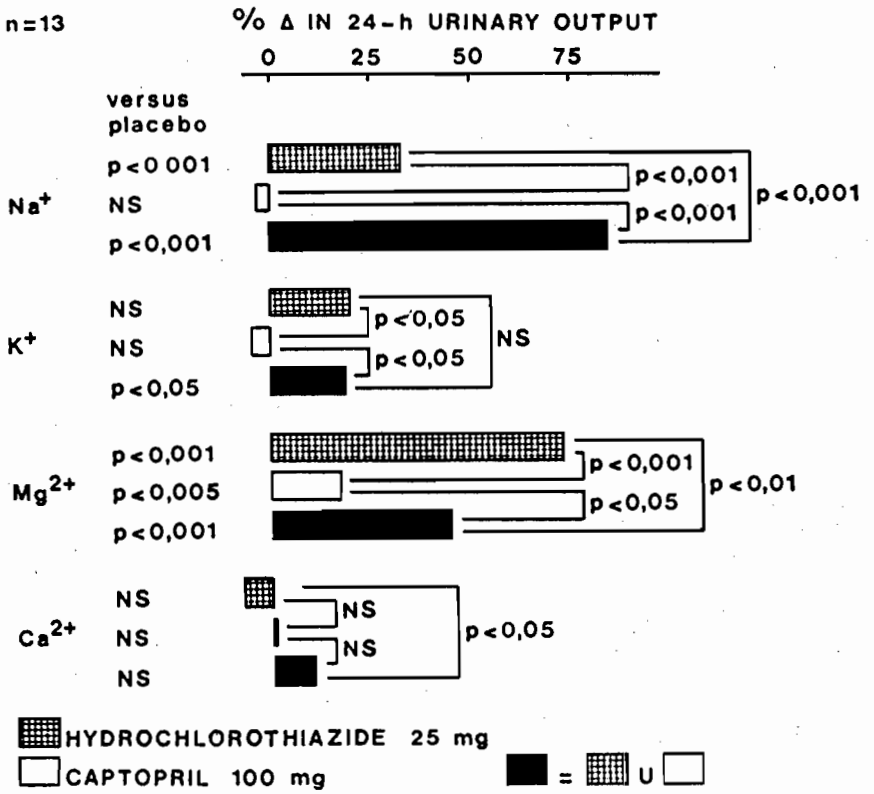

Fig. 4: Summary of the results from a study in which healthy volunteers were given single doses of hydrochlorothiazide 25 mg, of captopril 100 mg and of a combination of hydrochlorothiazide 25 mg and captopril 100 mg, double blind and in random order. Bars depict percentage changes in mean 24-h urinary electrolyte outputs after the active formulation with respect to mean post-placebo 24-h renal excretion. n = number of cases: NS = non significant. Adapted from [48] *Leary* et al., 1985, by courtesy of Raven Press/Journal of Cardiovasvular Pharmacology

diuretics or their combination. Meanwhile it would be prudent to exercise care in the management of hypertensives treated with ACE-inhibitors, especially in patients at risk of developing Mg^{2+} deficiency as a result of any of the factors listed in Tab. 2.

Calcium-antagonists and magnesium

Calcium antagonists such as verapamil, nifedipine and diltiazem are widely used in the treatment of hypertension and do not appear to interfere with the influx of Mg^{+} into myocardial cells [22, 23]. However experimental evidence exists that some related compounds, including prenylamine, terodiline, fendiline and perhexiline, may block the passage of both Ca^{2+} and Mg^{2+} across the sarcolemma. The clinical relevance of this observation is obscure at present but the possibility of causing intracellular Mg^{2+} deficiency should be born in mind when these compounds are administered together with diuretics or when any factor that may promote Mg^{2+} depletion coecists.

Magnesium deficiency and hypertension

Some experimental evidence exists to suggest that Mg^{2+} deficiency could be a factor of importance in the pathogenesis of essential hypertension. Decreased Mg^{2+} levels in blood and tissues potentiate vasoconstriction caused by humoral substances such as catecholamines and angiotensin II [3, 4, 33, 92] and Mg^{2+} deficiency accelerates the onset of hypertension in spontaneously hypertensive rats [7] and induces an elevation in blood pressure of Wistar rats [4].

Tab. 2: Conditions that may cause Mg^{2+} deficiency per se or aggravate Mg^{2+} deficiency induced by medication during the treatment of arterial hypertension

I. Decreased magnesium supply

- (a) Inadequate intake of Mg^{2+}
  - (i) Low Mg^{2+} content in drinking water or dietary constituents
  - (ii) Parenteral nutrition with low Mg^{2+} content
- (b) Reduced Mg^{2+} absorption
  - (i) Excessive intake of roughage, saturated fat or foodstuffs with high content of oxalate or phytate
  - (ii) Malabsorption syndromes including
    - — selective malabsorption of Mg^{2+}
    - — gluten enteropathy
    - — pancreatic insufficiency with steatorrhoea
    - — tropical sprue and
    - — radiation damage of the gastrointestinal tract
  - (iii) Short intestine syndromes including
    - — extensive resection of small bowel
    - — gastrojejunocolic fistulae
    - — jejunoileal bypass
  - (iv) Biliary fistulae
  - (v) Whipple's disease
  - (vi) Intestinal lymphectasia

II. Magnesium losses

- (a) Enteric
  - (i) Vomiting
  - (ii) Diarrhoea
  - (iii) Repetitive gastirc aspiration
  - (iv) Laxative abuse
- (b) Excessive sweating
- (c) Renal causes
  - (i) Renal inusfficiency with hypermagnesiuresis
  - (ii) Excessive intake of caffeine-containing beverages
  - (iii) High Na^{+} intake
  - (iv) Drug-induced hypermagnesiuresis due to diuretics, cisplatin, amphotericin B, carbenicillin, gentamicin, tricarcillin, cardiac glycosides, osmoticdiuretics
  - (v) Expansion of extracellular fluid volume
  - (vi) Renal tubular acidosis
  - (vii) Diuretic phase of acute tubular necrosis
  - (viii) Postobstructive polyuria
  - (ix) Hydronephrosis
  - (x) Essential familial hypermagnesiuresis
  - (xi) Essential sporadic hypermagnesiuresis
  - (xii) Postrenal transplantation
- (d) Excessive lactation

III. Conditions in which various factors coexist which negatively affect magnesium balance

- (a) Stress
- (b) Alcoholism
- (c) Hungry bone syndrome
- (d) Endocrine syndromes
  - (i) Hyperparathyroidism
  - (ii) Hyperthyroidism
  - (iii) Diabetes mellitus
  - (iv) Hyperaldosteronism
  - (v) Excess of glucocorticoids
- (e) Protein malnutrition
- (f) Phosphate deficiency
- (g) Metabolic acidosis
- (h) Hypercalcaemia
- (i) Acute pancreatitis
- (j) Third-term pregnancy
- (k) Exchange transfusion

However more recent studies have failed to confirm the findings in spontaneously hypertensive rats [25] and no correlation between arterial blood pressure and 24-hour urinary Mg^{2+} output was found in an extensive epidemological study carried out in man [36]. Two investigations carried out in large groups of hypertensives failed to show any derangement in plasma Mg^{2+} level [64, 93] although a recent study in black hypertensives found a weak inverse correlation between blood pressure and plasma or red cell Mg^{2+} levels (*H. Seftel,* personal communication).

Attempts have been made to determine whether the urinary Mg^{2+} losses induced by common diuretics compromise their antihypertensive effect to any extent. In one study it was found that significant mean drops in supine blood pressure occurred in patients chronically treated with common diuretics when supplementary Mg^{2+} (15 mmol.day^{-1}) was added to the therapeutic regimen [18]. This study was not prospective however and placebo for Mg^{2+} was not administered to the control group. Subsequent prospective studies failed to demonstrate that dietary supplementation with Mg^{2+} had any

significant effect upon arterial blood pressure when administered either alone or in combination with a diuretic [9, 78]. It therefore appears unlikely that Mg^{2+} deficiency should be considered of major importance in the aetiology, pathogenesis or management of most cases of arterial hypertension although it may be of relevance in individual patients and could contribute to morbidity and mortality from cardiac arrhythmias and infarction.

Magnesium deficiency and cardiovascular risk factors

Magnesium deficiancy has been incriminated as a coronary risk factor [3, 28]. Epidemiological studies in Finland and South Africa have indicated that the incidence of deaths ascribed to ischaemic heart disease correlates inversely with the concentration of Mg^{2+} in drinking water [34, 35, 41, 51]. Plasma Mg^{2+} concentration is significantly lower in patients with coronary artery disease diagnosed by arteriography than in patients with healthy arteries [53]. Evidence has also been presented that Mg^{2+} deficiency predisposes to significant cardiac arrhythmias [67].
These findings add emphasis to the importance of avoiding Mg^{2+} depletion during the prolonged treatment of arterial hypertension, particularly since raised blood pressure is a cardiovascular risk factor per se.

Diagnosis of magnesium deficiency

The clinical presentation of Mg^{2+} deficiency has been reviewed extensively [67] and includes the presentation of many non-specific signs and symptoms including anorexia, apathy, muscular weakness and fatigue. *Chvostek's* and *Trousseau's* signs may be present and cardiac arrhythmias, notably atrial fibrillation, ventricular and supraventricular extrasystoles can be the presenting feature of Mg^{2+} deficiency. Peripheral tremor involving muscles of the face, tongue and limb, ataxia, nystagmus, tetany and convulsions may occur. The existence of Mg^{2+} deficiency should be suspected and sought whenever therapy with a magnesiuretic has been prolonged beyond 4 months and particularly if dosage has been

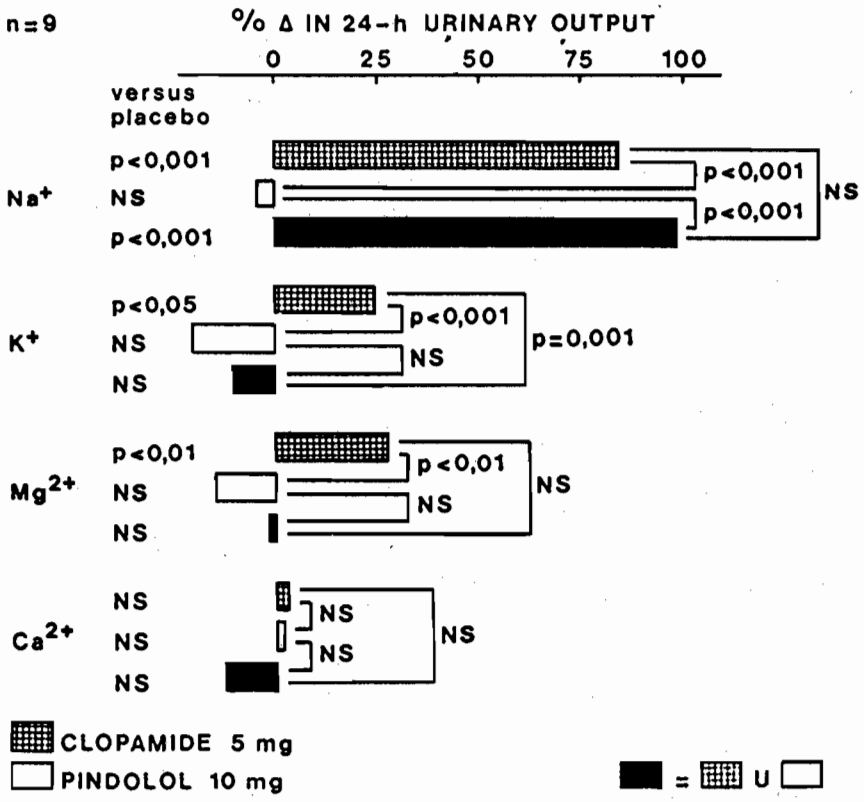

Fig. 5: Summary of the results from a study in which healthy volunteers were given single doses of clopamide 5 mg, of pindolol 10 mg and of a combination of clopamide 5 mg and pindolol 10 mg, double blind and in random order. Bars depict percentage changes in mean 24-h urinary electrolyte outputs after the active formulations with respect to mean post-placebo 24-h renal excretions. n = number of cases; NS = non-significant. Adapted from [80] *Reyes* et al., 1985 by courtesy of Magnesium-Bulletin

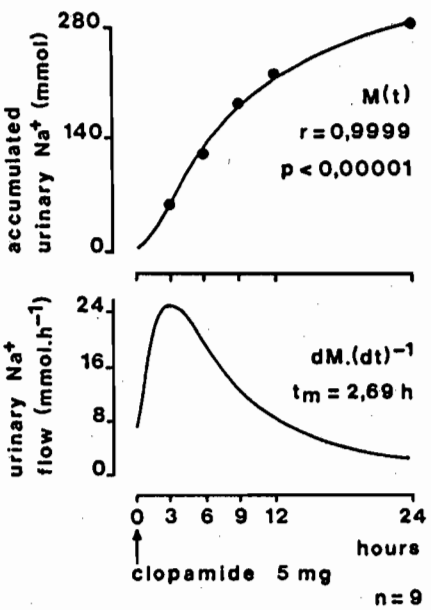

Fig. 6: Top: Mean accumulated urinary Na^+ output (dots) after administration of a single dose of clopamide 5 mg per os to nine healthy volunteers at time 0 (0800h). Bottom: Mean urinary Na^+ flow after administration of a single dose of clopamide 5 mg per os to nine healthy volunteers at time 0 (0800h). The graph has been evaluated as the derivative of the function in the top panel with respect to time (dM/dt). Any area between the curve and the abscissae axis and between any two times represents the amount of electrolyte excreted between the times that constitute the area limits. t_m is the time dosing to maximal flow. Adapted from [80] *Reyes* et al, 1985 by courtesy of Magnesium-Bulletin

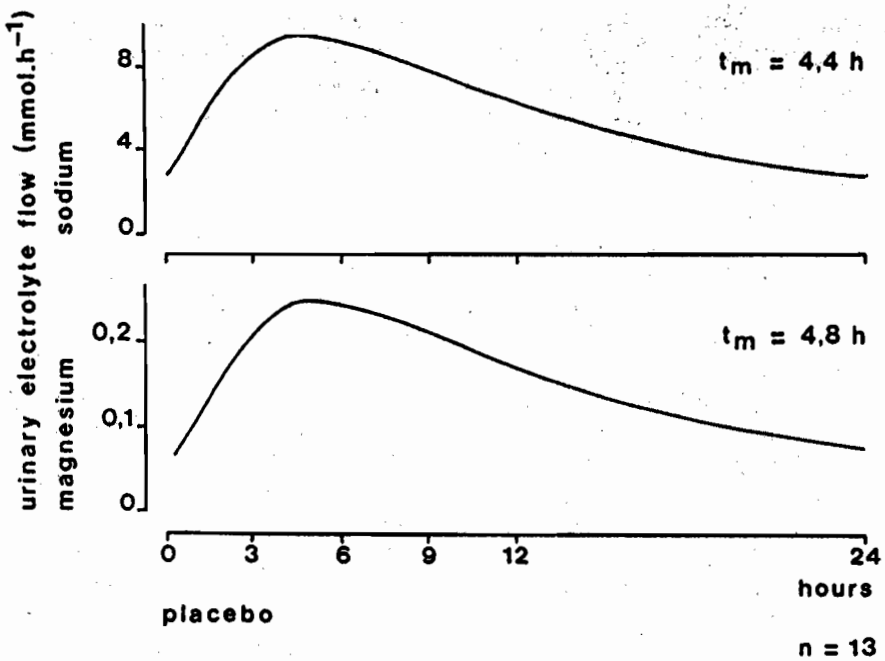

Fig. 7: Urinary Na^+ (top panel) and Mg^{2+} (bottom panel) flows after the administration of placebo to healthy volunteer subjects at hour 0 af the experiment (0800h). n = number of cases; t_m = time to maximal flow after dosing. Adapted from [77] *Reyes* and *Leary*, 1984d, by courtesy of Brazilian Journal of Medicine and Biological Research

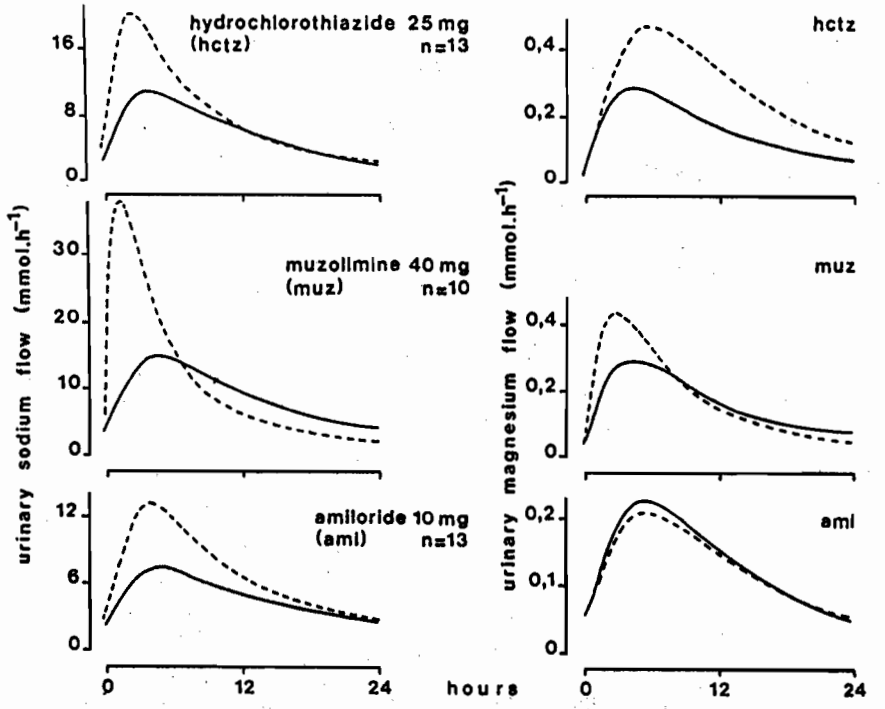

Fig. 8: Urinary Na^+ (left hand panel) and Mg^{2+} (right hand panel) flows after the separate administration of various diuretics (dashed lines) and of corresponding placebos (continuos lines) to healthy volunteer subjects at hour 0 of the experiments (0800-h). n = number of cases. From top to bottom, adapted from [48] *Leary* et al., 1985; [47] *Leary* et al., 1985 and [39] *Leary* et al., 1983, by courtesy of Raven Press Journal of Cardiovascular Pharmacology, Zeitschrift für Kardiologie and Current Therapeutic Research, respectively

high or other factors are present which favour the development of Mg^{2+} deficiencx (Tab. 2). There is no specific routine biochemical test which estimates total body Mg^{2+} with any accuracy but measurement of plasma Mg^{2+} concentration by atomic spectroscopy is of some assistance in the detection of Mg^{2+} deficiency which is usually diagnosed when total plasma Mg^{2+} concentration is below 0.75 $mmol.L^{-1}$ [17, 81]. However a normal serum Mg^{2+} level does not exclude somatic deficiency since Mg^{2+} is mobilised from bone into plasma during the initial stages of somatic depletion.

Prophylaxis and tretment of magnesium deficiency

It should be born in mind that Mg^{2+} deficiency develops in relatively few hypertensive patients treated for prolonged periods with magnesiuretic compounds; nevertheless good clinical practice demands that appropriate measures be taken to further limit the incidence of this condition. This may be achieved by correcting factors likely to induce Mg^{2+} deficiency (Tab. 2), selecting formulations that limit urinary Mg^{2+} losses, minimizing diuretic doses, and the administration of Mg^{2+} supplements. Magnesium salts should be used prophylactically in patients at risk of developing Mg^{2+} deficiency; doses of 7.5 – 15 $mmol.day^{-1}$ should be taken, divided between the main meals. Dosage may be doubled when evidence of frank Mg^{2+} deficiency occurs and can be given in the form of aspartate, chloride, citrate, gluconate, lactate or orotate salts which are absorbed to a similar extent [67].

When cardiac arrhythmias develop during diuretic treatment Mg^{2+} replacement is indicated; intravenous magnesium sulphate restores the intracellular concen-

trations of both Mg^{2+} and K^+ normal in patients with hypokalaemia and hypomagnesaemia secondary to prolonged diuretic therapy whereas simple K^+ replacement has no such effect on either cation [15, 16, 91]. The possibility of Mg^{2+} overdosage is remote, except in individuals with renal insufficiency.

Further measures which may be taken to limit Mg^{2+} losses in hypertensives treated with diuretics include the coadministration of K^+-retaining Mg^{2+}-sparing diuretics or the coadministration of a beta-adrenergic blocking agent. The coadministration of a K^+-retaining and a distal tubular diuretic diminishes the acute magnesiuresis caused by the common diuretic but may not fully compensate for the urinary losses of K^+ and Mg^{2+} which occur during prolonged therapy. [40, 44, 62, 82, 83, 89]. At present only the acute effects of pindolol upon magnesiuresis are known and it is uncertain whether prolonged therapy with this or other beta-adrenergic blockers will have beneficial effects upon urinary losses of Mg^{2+} [80].

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