# Diuretics and magnesium

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**Zusammenfassung**

Die chronische Gabe von Diuretika mit Angriffspunkt an der *Henle*schen Schleife oder am distalen Tubulus kann zur Mg-Verarmung des Körpers führen. Das resultierende Mg-Defizit destabilisiert die elektrische Erregbarkeit des Myokards und ist Hauptursache für das Auftreten von Arrhythmien nach Behandlung mit Diuretika. Der Mg-Mangel fördert die Entwicklung von Erkrankungen der Coronar- und Cerebralgefäße, das Auftreten von Arrhythmien während des akuten Myokardinfarktes und Störungen des Lipid- und Kohlenhydratstoffwechsels bei Therapie mit Diuretika. Diese unerwünschten Nebenwirkungen können vermieden werden durch Auswahl von Diuretika, die keine Mg-Verluste induzieren, durch Minimierung der Dosis, durch Optimierung der Na- und Mg-Aufnahme und — in einigen Fällen — durch Supplementierung mit Mg.

**Summary**

The chronic administration of common loop or distal tubular diuretics may lead to somatic depletion of Mg. The resultant deficiency of Mg destabilizes the myocardium electrically and is the principal cause of cardiac arrhythmias ascribed to diuretics. Mg deficiency positively contributes to the development of coronary artery and cerebrovascular diseases, to the occurrence of cardiac arrhythmias during acute myocardial infarction and to the derangements of lipid and carbohydrate metabolism that occur during treatment with diuretics. These adverse effects of diuretics can be avoided by selecting diuretic formulations that do not cause Mg deficiency, minimization of the diuretic dose, optimization of Na and Mg intakes and, in some cases, supplementation of Mg.

**Résumé**

L'administration chronique des diurétiques usuels (diurétiques d'anse ou diurétiques distaux) peut conduire à une déplétion somatique de Mg. Le deficit en Mg altère électriquement le myocarde et est la cause principale des arythmies cardiaques imputées aux diurétiques. Le deficit en Mg contribue au développement des maladies coronariennes et cérébrovasculaires ainsi qu'au développement d'arythmies cardiaques pendant l'infarctus aigu du myocarde et aux altérations du métabolisme lipidique et glucidique qui ont lieu pendant le traitement diurétique. La prévention de ces effets indésirables des diurétiques doit être effectuée par une sélection adequate de la substance diurétique, l'usage de doses minimales, l'ingestion optimale de Na et de Mg et l'administration de Mg chez certain malades.

Modern diuretics may be classified into three groups. Loop diuretics such as furosemide, ethacrynic acid, bumetanide, muzolimine and piretanide have their main site of renal action at a common acceptor in the thick ascending portion of the loop of *Henle* [74, 81]. The main sites of renal action for distal tubular diuretics, including thiazides, chlorthalidone, chlorexolone, indapamide and xipamide, are at specific acceptors for each substance, in the first portion of the distal convoluted tubule [74, 81]. The K-retaining diuretics spironolactone, amiloride and triamterene inhibit normal transparietal interchange between Na, which is reabsorbed, and K and H, which are excreted, in the final portion of the distal convoluted tubule [74, 81].

Common diuretics are defined as those principally acting at the loop of *Henle* or at the distal convoluted tubule. A standard diuretic dose of these drugs provokes a natriuresis equivalent to that induced by 40 mg of furosemide (loop diuretics) or to 50 mg of hydrochlorothiazide (distal tubular diuretics), when these drugs are administered orally to healthy volunteers under controlled experimental conditions [74].

The chronic administration of common diuretics at standard doses may give rise to diverse cardiac arrhythmias, including ventricular fibrillation, or sudden death, and may also increase the risks of myocardial infarction and of arrhythmias complicating acute myocardial infarction [74, 81].

Classically, K-deficiency caused by common diuretics has been incriminated as the principal pathogenic factor of arrhythmias provoked by these drugs [62, 65, 68]. However, K deficiency is only a contributing factor, whereas the principal determinant of diuretic-induced cardiac arrhythmias is Mg deficiency, which is secondary to the hypermagnesiuria induced by common diuretics [18—23, 74, 82—85, 90, 95, 105—107]. In all cases of cardiac arrhythmias unequivocally due to common diuretics, in which appropriate laboratory analyses were carried out, Mg deficiency was identified as the causative factor and the supplementation of Mg suppressed the arrhythmia, irrespective of overall somatic K status [19, 23, 95].

It is possible that the well known fact that effective control of essential hypertension by monotherapy with distal tubular diuretics does not reduce the incidence of sudden death in these patients could be explained by the deficiency of Mg which these drugs cause [83].

## Hypermagnesiuria and magnesium deficiency provoked by diuretics

The effects on 24-hour urinary Mg output of single standard doses of several common diuret-

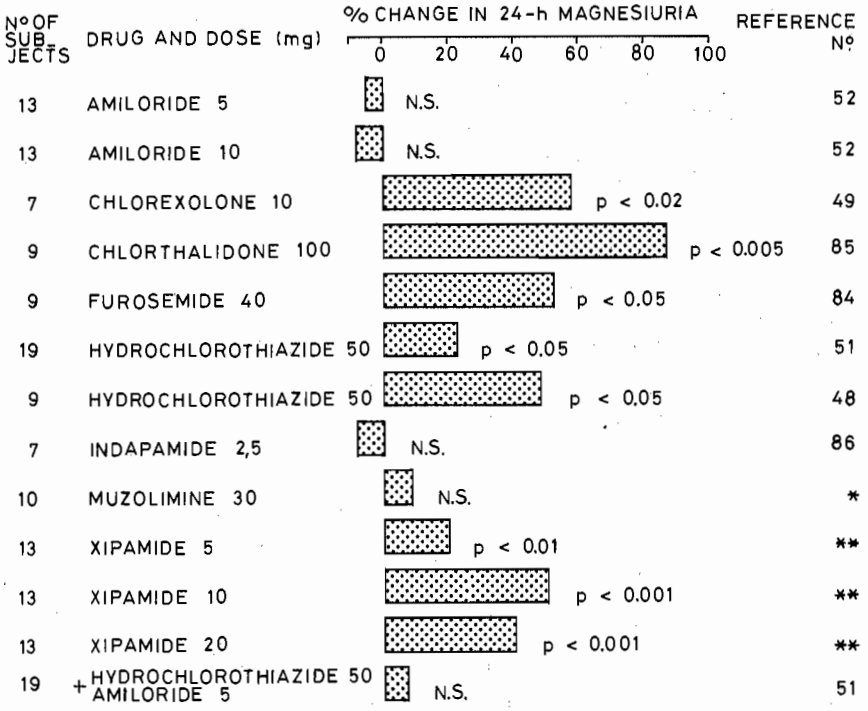


Fig. 1: Summary of the results from several studies in which healthy volunteers were given single doses of diuretic formulations. The bars depict percentual changes in 24-hour urinary Mg output after these diuretics with respect to control 24-hour magnesiuria. N.S.: non significant. *Leary, W. P., Reyes, A. J., van der Byl, K.: Curr. Ther. Res., in press. **Reyes, A. J., Leary, W. P.: manuscript in preparation.

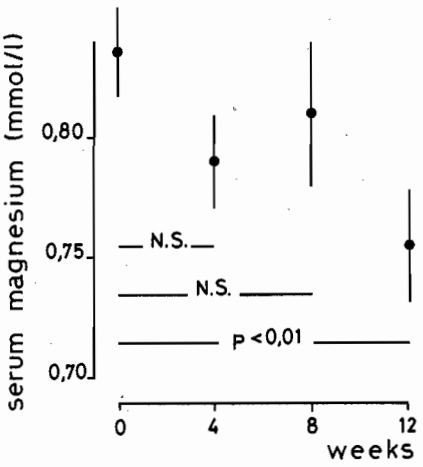


Fig. 2: Changes in magnesaemia during the monotherapeutic treatment of nine hypertensive patients with piretanide 12 mg/day. Mean ± S.E.M.. N.S.: non significant. From Leary and Reyes [46], by courtesy of South African Medical Journal.

ics were studied in normal, biologically equivalent, volunteers under controlled conditions. Chlorexolone, chlorthalidone, furosemide, hydrochlorothiazide and xipamide induced significant hypermagnesiuria in the 24-hour period after dosing with active medication (Fig. 1). The loop diuretic muzolimine 30 mg, the distal convoluted tubular diuretic indapamide 2.5 mg and the K-retaining diuretic amiloride 5 or 10 mg did not affect urinary Mg output significantly (Fig. 1). The combination of hydrochlorothiazide 50 mg and amiloride 5 mg also had no effect on 24-hour magnesiuria (Fig. 1). All tested formulations significantly increased 24-hour urinary Na output and chlorexolone, chlorthalidone, hydrochlorothiazide, indapamide, muzolimine and xipamide increased 24-hour urinary K output significantly.

No data exist on the effects chronic administration of diuretics has on total bodily Mg. In a study where plasma Mg was measured before and during treatment with the loop diuretic piretanide 12 mg/day in nine patients, the variable was found to be significantly decreased after twelve weeks of therapy [46] (Fig. 2). Hydrochlorothiazide 50 mg (9 patients) or a combination of hydrochlorothiazide 50 mg and amiloride 5 mg (12 patients) reduced plasma Mg significantly in hypertensive patients given these diuretics as monotherapy after an average of 20 weeks (*Leary, W. P., Reyes, A. J., van der Byl, K.:* unpublished).

## Mechanism of magnesium deficiency provoked by diuretics

Normal urinary Mg output ranges from 4 to 8 mmol/day (100—400 mg/day). Most filtered Mg is reabsorbed in the nephron, 20—30 % at the proximal convoluted tubule, 50—60 % at the thick ascending portion of the loop of *Henle* and 1—5 % at the distal convoluted tubule [69—71]. Parathormone promotes Mg reabsorption at the loop of *Henle* and, perhaps, at the distal convoluted tubule [56, 66, 71]. The kidney, which is the principal regulatory organ of Mg metabolism, handles this cation independently from Cl, Na and K [56, 66, 69—71].

### *Loop diuretics*

Loop diuretics block the transparietal reabsorption of Mg at the thick ascending portion of the loop of *Henle* [69, 71]. This blockade is independent from that of Cl reabsorption at the same anatomical level, which accounts for the natriuretic effect of loop diuretics [56, 71]. After the administration of placebo to normal volunteers, the mean Cl, Na, fluid and Mg urinary flow curves, derived from experimental data according to the *Reyes* and *Leary* mathematical model [78], indicate that the time courses of all these urinary excretions are parallel (Fig. 3). After the administration of a loop diuretic to the same probands, urinary Mg flow is delayed with respect of those of Cl, Na and fluid [84] (Fig. 4). This fact sug-

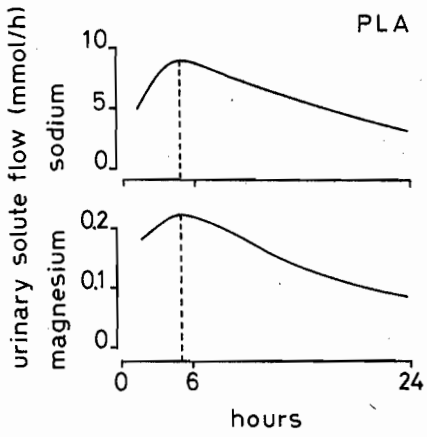


Fig. 3: Mean urinary Na and Mg flows after the administration of placebo per os to nine healthy volunteers at time 0 of the experiment (08.00). The time courses of natriuria and magnesiuria are similar; their peaks therefore practically coincide in time. From Reyes and Leary [85], by courtesy of Current Therapeutic Research.

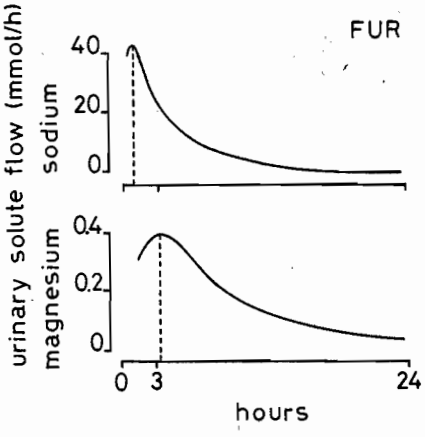


Fig. 4: Mean urinary Na and Mg flows after the administration of furosemide 40 mg per os to nine healthy volunteers at time 0 of the experiment (08.00). The time course of magnesiuria is delayed with respect to that of natriuria. From Reyes and Leary [84], by courtesy of Current Therapeutic Research.

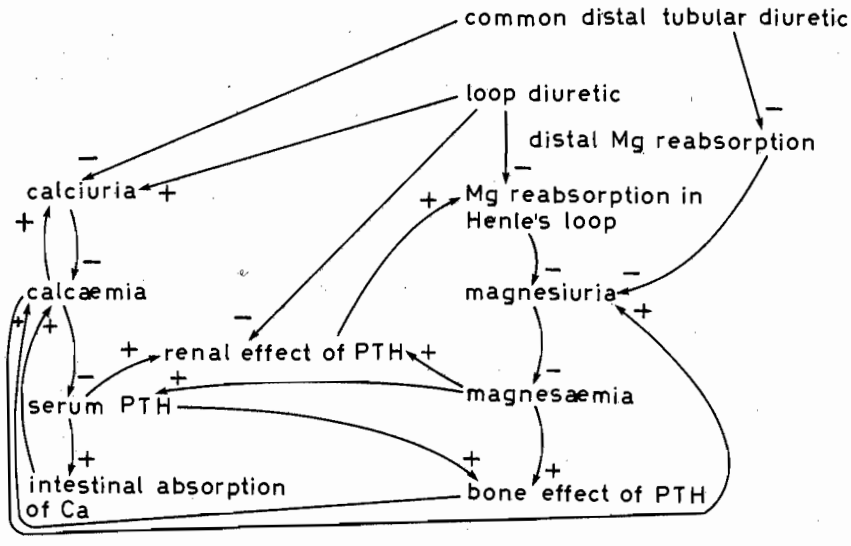


Fig. 5: Causal diagram of the determination of Mg deficiency provoked by loop and distal tubular diuretics. The diagram depicts changes (+: augmentation; −: diminution) resulting from increases in the variables at which arrows start (system dynamics notation). PTH: parathyroid hormone. From Reyes [73], by courtesy of La Prensa Médica Argentina.

gests that a slow mechanism contributes to the hypermagnesiuria induced by loop diuretics, in addition to the direct blockade of the reabsorption of the cation [82].

Loop diuretics provoke hypercalciuria [81, 87] which decreases calcaemia and thus increases serum (s) parathormone (PTH) [24]. PTH mobilizes Ca and Mg from bone, increasing the amount of Mg available for renal excretion in this manner, and perpetuating hypermagnesiuria [82]. Mg deficiency ensues unless its exogenous supply is increased. Mg deficiency reveals itself as hypomagnesaemia only 8—15 weeks after the initiation of diuretic treatment [46] because of Mg mobilization from bone to plasma [82].

Mg deficiency decreases the release of PTH since the cation normally activates parathyroid adenylate cyclase by competition with Ca at the modulating site of the enzyme or by promotion of the synthesis of endogenous guanine nucleotides [54]. In addition, Mg deficiency causes resistance to the action of PTH in bone and in the kidney [27, 28, 92), apparently because it obtunds interaction between the hormone's receptor and adenylate cyclase, an enzyme which is positively influenced by PTH [99]. Thus, Mg deficiency decreases sPTH and increases renal and bone resistance to it; both these facts tend to increase hypermagnesiuria (Fig. 5). Moreover, furosemide has been found to directly diminish renal sensitivity to PTH [102]. The diminution in sPTH and bone resistance to it limit Mg and Ca mobilization from its main store, thus reinforcing hypocalcaemia, which diminishes magnesiuria directly, i.e. independently from PTH [70, 71]; this compensating mechanism is however of limited quantitative importance. The decreases in sPTH and in its renal effect decrease the activity of renal 1-hydroxylase; the synthesis of 1,25 ($OH_2$) D3 is therefore decreased and hypocalcaemia aggravated. Hypocalcaemia stimulates the activity of renal 1-hydroxylase and consequently the synthesis of 1,25 ($OH_2$) D3; hypocalcaemia and hypomagnesaemia are thus partially compensated for; however, this mechanism has no quantitative significance.

Although muzolimine 30 mg did not increase 24-hour urinary Mg output significantly (Fig. 1), it delayed urinary Mg flow with respect to Na in the same manner as furosemide 40 mg (*Leary, W. P., Reyes, A. J., van der Byl, K.:* Curr. Ther. Res., in press). This indicates that muzolimine, at its standard diuretic dose, brings into play the mechanisms that account for loop-diuretic-induced hypermagnesiuria. The

possibility that this formulation could provoke significant depletion of somatic Mg upon prolonged administration should therefore be evaluated. Higher doses of this substance could be expected to induce hypermagnesiuria acutely.

*Distal convoluted tubular diuretics*

Hypermagnesiuria provoked by diuretics acting at the distal convoluted tubule cannot be explained solely by direct blockade of the transparietal reabsorption of the cation since only 1-5 % of filtered Mg is reabsorbed in the distal tubule. In experiments similar to those described for furosemide, significant dephasing was found between the time courses of urinary Mg and urinary Cl, Na and fluid after the administration of diuretics such as hydrochlorothiazide [48] (Fig. 6), chlorthalidone, xipamide (*Reyes, A. J., Leary, W. P.:* unpublished) and chlorexolone [49].

These diuretics cause hypocalciuria [11], followed by hypercalcaemia, which increases magnesiuria [70] and reduces sPTH [70]. The decrease in sPTH diminishes the reabsorption of Mg in the loop of *Henle,* thus

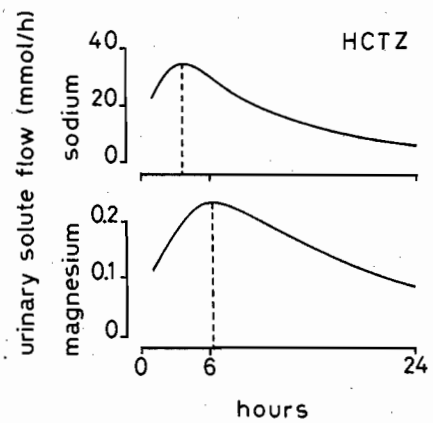


Fig. 6: Mean urinary Na and Mg flows after the administration of hydrochlorothiazide 50 mg per os to nine healthy volunteers at time 0 of the experiment (08.00). The time course of magnesiuria is retarded with respect to that of natriuria. From Leary and Reyes [48], by courtesy of Current Therapeutic Research.

further increasing magnesiuria. The subsequent mechanisms whereby distal convoluted tubular diuretics provoke hypermagnesiuria are similar to those associated with loop diuretics (Fig. 5).

Indapamide 2.5 mg probably did not provoke hypermagnesiuria because the dose administered, which exhibits the maximal antihypertensive effect of this substance [76], is well below its standard diuretic dose. However, after indapamide 2.5 mg there was a delay in urinary Mg flow with respect to that of Na [86], which suggests that this diuretic provokes hypermagnesiuria at higher doses.

*Potassium-retaining diuretics*

The K-retaining diuretic amiloride reduced urinary Mg excretion, although this reduction was statistically not significant, and it did not alter the time course of Mg urinary flow in normal individuals [52]. When a combination of amiloride 5 mg and hydrochlorothiazide 50 mg was administered to healthy volunteers there was also no significant change in Mg output [51] (Fig. 1). This suggests that amiloride induces Mg reabsorption and therefore acts as a Mg-sparer when the amount of the cation passing through the distal convoluted tubule is increased by the action of common diuretics at more proximal nephronal sites. This effect of the amiloride and hydrochlorothiazide combination only occurs upon acute administration; its prolonged administration causes hypomagnesaemia (*Leary, W. P., Reyes, A. J., van der Byl, K.:* unpublished).

## Pathogenesis of cardiac arrhythmias provoked by common diuretics

The following description has its point of departure at the electrically "resting" myocardial cell. The processes described are summarized in Figs. 7 and 8.

Treatment with common diuretics may significantly diminish the intramyocardial content of Mg [23, 64, 95, 107]. This decreases the activity of the $Na^+$, $K^+$-ATPase which accounts for the generation of energy used for the active transport of K into the cell and of Na from it (Na-K pump), since $Na^+$, $K^+$-ATPase requires Mg as a cofactor [23, 67]. In consequence, the intramyocardial concentration of Na increases and that of K decreases when Mg deficiency is present (Fig. 7). The reduction in the intracellular concentration of K is aggravated by somatic K expoliation which results from the hyperkaliuresis provoked by common diuretics [46, 48, 49, 61, 62, 79, 81, 84—86]. Diuretics increase the amount of Na reaching the final portion of the distal convoluted tubule and therefore the normal interchange between Na and K, H is increased. In addition, hyponatraemia and the relative decrease in heart output, elicited by the natriuretic action of diuretics, increase aldosteronaemia which further elevates the Na — K, H interchange in the distal convoluted tubule [37, 81, 100]. In familial hypokalaemic alkalosis with tubulopathy [35] hypermagnesiuria occurs in association with hyperaldosteronaemia and hypomagnesaemia increases aldosteronaemia independently from the renin-angiotensin system, but it is unlikely that these mechanisms operate during the treatment of ordinary patients with common diuretics [56]. The increase in proton excretion in urine elevates extracellular pH, thus facilitating the entrance of K into the cell by diffusion; however, the factors that decrease intracellular K (increased kaliuresis, increased concentration gradient between the cell and the milieu intérieur and decrease in the $Na^+$, $K^+$-ATPase activity) predominate.

Cytosolic Ca concentration within the myocardium increases

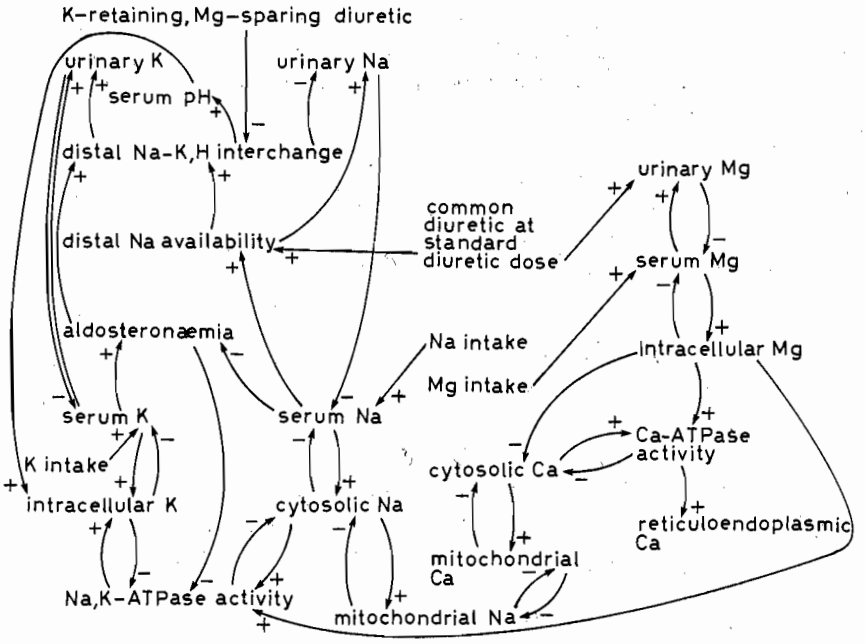


Fig. 7: Causal diagrams of the principal mechanisms whereby diuretics alter the intramyocardial concentrations of Mg, K, Ca and Na. The possibilities of several prophylactic and therapeutic interventions are also shown. The diagram depicts changes (+: augmentation; −: diminution) resulting from increases in the variables from where arrows depart (system dynamics notation). From Reyes [73], by courtesy of La Prensa Médica Argentina.

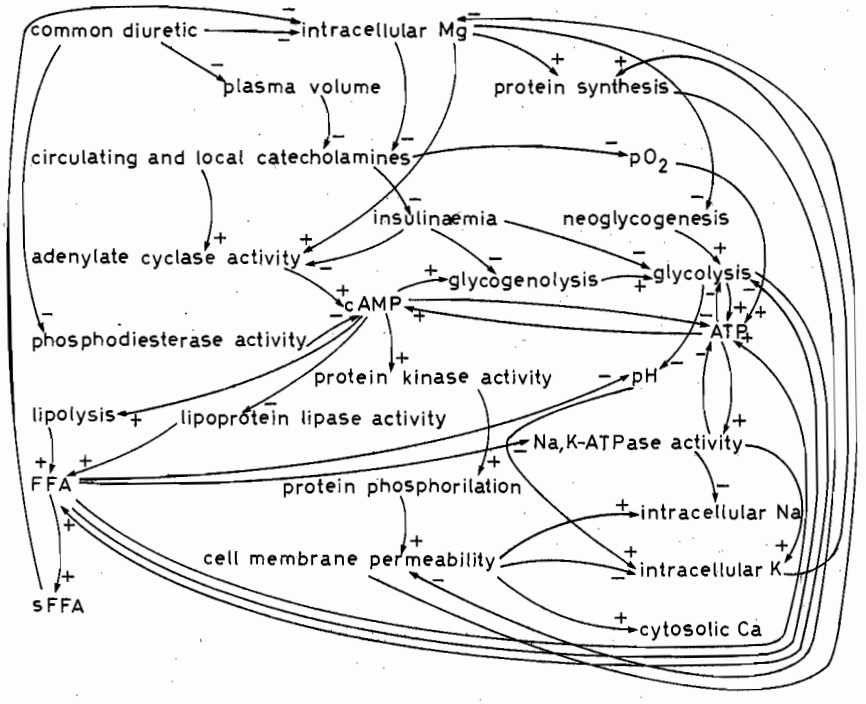


Fig. 8: Causal diagram of the complementary mechanisms whereby diuretics alter the intramyocardial concentrations of Mg, K, Ca and Na. The diagram depicts changes (+: augmentation; −: diminution) resulting from increases in the variables at which arrows depart (system dynamics notation). s: serum; FFA: free fatty acids. From Reyes [73], by courtesy of La Prensa Médica Argentina.

during Mg deficiency [105]. The increase in cytosolic Na secondary to reduced Na-K pump activity causes the transmitochondrial interchange of Na and Ca to rise so that Na passes into the mitochondria and Ca from them into the cytosol. The fall in intracellular Mg concentration decreases the activity of the Mg-dependent Ca-ATPase that accounts for the active transport of Ca from the cytosol into the endoplasmic reticulum, thus augmenting cytosolic Ca. Furthermore, the decrease in intracellular Mg leads to a net increase in Ca inflow across the sarcolemma, thus further elevating the cytosolic concentration of Ca [2]. The falls in Mg and K concentrations and the increases in cytosolic Na and Ca within the myocardium are the prime factors underlying the occurrence of cardiac arrhythmias during treatment with common diuretics given that all these ionic derangements destabilize the sarcolemma electrically, increasing myocardial excitability.

Further mechanisms exist which are not as important as those already described but contribute to the intramyocardial electrolyte disturbances provoked by diuretics (Fig. 8). The haemodynamic effect of diuretics increases the secretion of catecholamines by the adrenals. The decrease in intracellular Mg and the increase in cytosolic Ca reinforce this secretion and also augment the release of catecholamines by the sympathetic nerve endings [3, 4, 6]. Catecholamines activate adenylate cyclase and promote the synthesis of cyclic adenosine monophosphate (cAMP) from adenosine tryphosphate (ATP). The increased adenylate cyclase activity is reinforced because catecholamines decrease the secretion of insulin, which normally inhibits the activity of the enzyme. A decrease in intracellular Mg would cause a fall in the activity of adenylate cyclase, since Mg

promotes the activity of the enzyme directly and is a cofactor for enzymes involved in the cyclation of guanosine nucleotide which precedes the activation of adenylate cyclase [67]; however, the overall effect of the various factors involved is a net increase in the activity of adenylate cyclase [25]. The increase in cAMP availability is promoted by diuretics like hydrochlorothiazide [31] that inhibit the activity of phosphodiesterase, the enzyme which catalyses cAMP. The amount of cAMP produced depends on ATP availability. Catecholamines reduce tissue $pO_2$ and thus decrease the amount of ATP synthesized; however, increased glycolysis and lipolysis secondary to the rise in cAMP (Fig. 8) provide ATP via the production of free fatty acids (FFA).

An increase in ATP tends to diminish glycolysis since it reduces the activity of phosphofructokinase, which catalyses the rate limiting step of the glycolytic chain. However, glycolysis is stimulated by the cAMP-dependent activation of the glycogenolytic enzyme phosphatase and also because the decrease in intracellular Mg activates phosphoenol pyruvate carboxykinase, an enzyme that catalyses glyconeogenesis [59]. FFA bind ionic Mg in plasma thus removing it from the pool of ionic Mg which is transferable to the cell [30]. This perpetuates and aggravates the intracellular Mg deficiency provoked by diuretics.

Increased cAMP decreases the activity of lipoprotein lipase, thus reducing FFA liberation. Raised FFA levels decrease the activity of $Na^+$, $K^+$-ATPase, further altering the intramyocardial electrolyte balance [83]. cAMP also activates cellular protein kinase, which promotes the phosphorylation of sarcolemmal proteins; the cell membrane permeability to Ca, Na and K and Mg is thus increased in favour of their electrochemical gradients. Consequently, the intramyocardial concentrations of Ca [3] and Na rise and those of Mg and K fall. This is aggravated because protein synthesis is altered in Mg deficiency, since the cation acts as a cofactor for enzymes involved in transcription and because the fall in intracellular K also affects protein synthesis.

## Diuretics, magnesium deficiency and coronary and cerebrovascular diseases

Magnesium deficiency has been identified as a coronary risk factor.

The incidence of coronary heart disease varies widely between geographical regions and serious epidemiological studies have been carried out in order to identify variables that could explain these differences. In Finland [44, 53] and in South Africa [50] it was found that the incidence of death ascribed to ischaemic heart disease is inversely correlated with the concentration of Mg in drinking water. The level of Mg in drinking water ranges from 0.5 to 30 mg/l in different regions and is taken as an index of the Mg content of foods produced in the same geological area. Post mortem studies in England have demonstrated significantly reduced intramyocardial and coronary arterial wall Mg levels in road accident victims who lived in areas with Mg-deficient water supplies [16].

Plasma Mg concentration is significantly lower in patients with moderately severe coronary heart disease, diagnosed by arteriography, than in subjects with mild or absent radiographic changes [55].

Experimentally, Mg deficiency increases coronary [2-4, 96, 101-103] and cerebrovascular tone [6, 7] whereas Mg supplementation has a corrective effect. Mg deficiency increases vascular reactivity to catecholamines, angiotensins, K, serotonin, vasospastic peptides and neurohumoral stimuli and attenuates vasodilatation induced by prostaglandins or isoproterenol [2]. Mg and verapamil block the same Ca-entrance channel to the vascular smooth muscle cell [103]. The administration of Mg accelerates the rate of myocardial recovery from ischaemia in experimental animals [10].

Experimental Mg deficiency induces characteristic structural alterations in the myocardium [36] and in skeletal muscle [88]. In myocardial fibres, there is enlargement of the interstitial space of the transverse tubular system, a substance, possibly calcium phosphate, precipitates in vesicles of the longitudinal system of the endoplasmic reticulum and mitochondrial oedema with loss of mitochondrial matrix occurs. The interstitial space is enlarged, filaments and fibres of isolated collagen are seen in the vicinity of the interstitial capillaries and the fibrocyte endoplasmic reticulum is increased [36].

Stress increases catecholamine release and therefore induces Mg deficiency, which further augments catecholamine levels [13]. Stress has been experimentally found to provoke hypermagnesiuria [5] and stressing factors, like noise, deplete somatic Mg stores [13, 41]. Type-A behaviour [5], stress [13], catecholamines [13] and alterations in plasma lipids [72] potentiate each other as factors determining Mg deficiency and this interplay could explain the high incidence of coronary heart disease in the population with type-A behaviour.

When diuretics are administered to persons under stress or with coronary heart disease, particular care should be exercised to prevent the development of Mg deficiency.

## Diuretics, magnesium deficiency and hypertension

The possibility that Mg deficiency could contribute to the

development of arterial hypertension has been postulated on the basis of indirect experimental evidence [3]. However, no adequate epidemiological studies on the relationship between the incidence of hypertension and dietary Mg content exist [58].

In a study of hypertensive patients chronically treated with diuretics and with stable blood pressure values, it was found that subjects presented hypomagnesaemia; oral Mg supplementation in these patients produced both an increase in magnesaemia and a significant reduction in blood pressure [18]. This suggests that the antihypertensive effect of diuretics may be hampered by the decrease in somatic Mg which these substances induce. Plasma Mg concentration must be measured in hypertensive patients treated with common diuretics, and oral Mg supplements should be prescribed in cases of hypomagnesaemia before considering the effect of a diuretic maximal and adding another antihypertensive to the therapeutic regime.

## Diuretics, magnesium deficiency and acute myocardial infarction

The myocardial content of Mg has been found to be low in necrotic and perinecrotic zones [14], both in necropsy specimens and after coronary artery ligation in several species. Ventricular arrhythmias occurring during acute myocardial infarction respond better to Mg than to other antiarrhythmic agents [14, 63, 90]. Consequently, an appropriate therapeutic regime for patients treated with common diuretics who develop myocardial infarction, or to whom diuretics are administered during the acute phase of myocardial infarction, should usually include supplementary Mg administered orally or parenterally.

## Diuretic treatment, alterations in lipid and carbohydrate metabolisms and magnesium deficiency

Common loop and distal tubular diuretics generally provoke significant alterations in plasma lipids, when they are administered at standard diuretic doses to normal volunteers or hypertensive patients for more than 4 weeks. The changes consist of increases in total cholesterol [8, 26, 32, 35, 43, 46, 60] and/or triglycerides [8, 26, 35, 43, 45, 87] and of increases of the beta/alpha lipoprotein (LDL/HDL) ratio [32—34]. The alterations in plasma lipids are generally considered to increase the risk of cardiovascular disease. It is possible that Mg depletion is one of the factors leading to diuretic-induced dyslipaemias [80], since similar derangements of lipid metabolism occur in experimental Mg deficiency when animals are fed a high lipid or carbohydrate diet. Most investigations of the effects which diuretics have on lipid metabolism [8, 12, 26, 32—35, 43, 46, 60, 89, 104] have been biased by improper control of diet or failure to take other factors, such as familial history of diabetes or dyslipaemia, into account. Some of the effects of diuretics on lipid metabolism may be explained by the increase in catecholamines elicited by these drugs (Fig. 8); other effects could be related to the alteration in protein synthesis provoked by diuretics through increased K and Mg excretion (Fig. 8).

Both diuretics [31] and Mg deficiency reduce glucose tolerance thus causing a pathophysiological picture that resembles diabetes mellitus, a condition that is usually accompained by depletion in bodily Mg stores and that may be aggravated by diuretics or by Mg deficiency of any origin [42]. Patients with dyslipaemias induced by diuretics have been shown to respond favourably to supplementation of the diet with magnesium chloride tablets (*Davis, W. H., Warren, A.:* personal communication; *Reyes, A. J., Acosta-Barrios, T. N., Leary, W. P.:* unpublished).

## Magnesium deficiency provoked by diuretics clinical

It is difficult to diagnose Mg deficiency in its early stages [15, 20, 25, 27, 29, 39, 91, 93]. Its existence should be suspected when diuretic treatment in standard doses has been prolonged, especially if any other factor exists that may precipitate or aggravate diuretic-induced Mg deficiency or cause Mg deficiency per se (Table I). Many of these factors may also provoke K deficiency, which frequently coexists with Mg deficiency in patients treated with diuretics.

Clinical manifestations of Mg deficiency include anorexia, nausea, apathy, muscular weakness, fatigue, excitation and, in some cases, delirium or coma. Other clinical signs are tetany, peripheral tremor involving muscles of the tongue, face and limbs, ataxia, vertigo, lateral and vertical nystagmus, tetany and convulsions. Occasionally positive Chvostek and Trousseau signs, myoclonia or spontaneous carpopedal spasms occur. Advanced Mg deficiency may be confused with hypocalcaemia. The most frequent cardiac arrhythmia is atrial fibrillation, followed by ventricular and supraventricular extrasystoles [95] and ventricular fibrillation. The electrocardiographic signs of Mg deficiency are nonspecific prolongation of the PQ, QTc and QUc intervals and flattening of the T waves [17]. Muscular derangements of the inferior portion of the oesophagous may lead to dysphagia.

Microcytic anaemia with decreased erythrocytic half life, reticulocytosis and spherocytosis may be present in blood.

Hypocalcaemia and hypokalaemia resistant to supplementa-

*Table I: Conditions that may provoke magnesium deficiency per se or may precipitate or aggravate magnesium deficiency during diuretic treatment. Adapted from Reyes [73], by courtesy of La Prensa Médica Argentina.*

| | |
|---|---|
| 1. | Conditions in which Mg supply to the milieu intérieur is decreased. |
| 1.1. | Inadequate intake. |
| 1.1.1. | Low Mg content in all foods. |
| 1.1.2. | Diet poor in Mg. |
| 1.1.3. | Decreased food intake. |
| 1.1.4. | Parenteral nutrition with low Mg content. |
| 1.2. | Altered absorption. |
| 1.2.1. | Malabsorption syndromes. |
| 1.2.1.1. | Gluten enteropathy. |
| 1.2.1.2. | Pancreatic insufficiency with steatorrhoea. |
| 1.2.1.3. | Tropical sprue. |
| 1.2.1.4. | Other. |
| 1.2.2. | Extensive enteral resection. |
| 1.2.3. | Biliary and enteric fistuli. |
| 1.2.4. | Excessive intake of oxalate and phytate. |
| 2. | Conditions in which Mg losses are increased. |
| 2.1. | Enteric. |
| 2.1.1. | Vomiting. |
| 2.1.2. | Diarrhoea. |
| 2.1.3. | Repetitive gastric aspiration. |
| 2.2. | Excessive sweating. |
| 2.3. | Renal. |
| 2.3.1. | Renal insufficiency with hypermagnesiuria. |
| 2.3.2. | Osmotic diuresis (glucose, mannitol, urea). |
| 2.3.3. | Alcohol. |
| 2.3.4. | Drug-induced hypermagnesiuria. |
| 2.3.4.1. | Antineoplastics: cisplatin. |
| 2.3.4.2. | Antibiotics: amphotericin B, carbenecillin, gentamicin, ticarcillin. |
| 2.3.4.3. | Cardiac glycosides. |
| 2.3.5. | Chronic parenteral nutrition with liquids. |
| 2.3.6. | Renal tubular acidosis. |
| 2.3.7. | Diuretic phase of acute tubular necrosis. |
| 2.3.8. | Postobstructive polyuria. |
| 2.3.9. | Essential familial hypermagnesiuria. |
| 2.3.10. | Essential sporadic hypermagnesiuria. |
| 3. | Conditions in which various factors coexist. |
| 3.1. | Hungry bone syndrome. |
| 3.2. | Hyperparathyroidism. |
| 3.3. | Hyperthyroidism. |
| 3.4. | Excessive lactation. |
| 3.5. | Protein malnutrition. |
| 3.6. | Diabetes mellitus. |
| 3.7. | Phosphate deficiency. |
| 3.8. | Metabolic acidosis. |
| 3.9. | Primary hyperaldosteronism. |
| 3.10. | Hypercalcaemia of any origin. |
| 3.11. | Acute pancreatitis. |
| 3.12. | Third term pregnancy. |

tion therapy have been reported in association with Mg deficiency and metabolic alkalosis also occurs. Total plasma lipids may be elevated [15, 20, 25, 27, 29, 39, 92, 93].

No routine procedure exists for the evaluation of total bodily Mg levels. Measurement of the plasma Mg concentration is the procedure of choice for diagnosing Mg deficiency, although experimental error is such that atomic absorption spectrometry is the only acceptable method routinely available at the moment. Atomic spectrometry measures total plasma Mg; diffusible Mg may be evaluated, in plasma and tissues, by means of a selective electrode [40], which is not yet used in the clinical laboratory.

When the total plasma Mg concentration, referred to as magnesaemia, is less than 0.75 mmol/l (1.50 mEq/l) Mg deficiency is conventionally diagnosed [20, 92]. The upper limit of normality is 1.05 mmol/l (2.10 mEq/l). It must be stressed that a normal plasma Mg level does not necessarily exclude somatic Mg deficiency, since in the early stages of the condition Mg is mobilized from bone retarding any fall in Mg concentration.

The concentration of Mg in striated muscle has been used to evaluate the ion content in soft tissue [23], but it bears no linear relationship to myocardial Mg, since the cation is retained in the myocardium more readily than in skeletal muscle. Lymphocytes provide an adequate means for estimating somatic Mg status, because they are metabolically active, can be studied repeatedly [94] and intralymphocytic and intramyocardial Mg contents correlate linearly.

## Prophylaxis and treatment of magnesium deficiency and associated metabolic derangements during diuretic treatment

### *Selection of the diuretic formulation*

The results of the experimental series summarized in Fig. 1 and data from literature identify those currently available diuretic formulations which are unlikely to provoke Mg deficiency.

When a loop diuretic is chosen for prolonged treatment, muzolimine 30 mg should usually be selected in preference to furosemide 40 mg which has been found to induce Mg deficiency and cardiac arrhythmias when it is administered chronically [95].

When an antihypertensive diuretic is needed, selection from the formulations tested so far should be limited to indapamide 2.5 mg or the combination of hydrochlorothiazide 50 mg + amiloride 5 mg. Indapamide 2.5 mg provokes hyperkaliuresis but in telemetric studies it has not been found to induce cardiac arrhythmias during chronic administration [38]. Moreover, indapamide 2.5 mg does not alter lipid [104] or carbohydrate [91] metabolism. The hydrochlorothiazide-amiloride combination does not provoke hyperkaliuresis or hypermagnesiuresis when administered acutely and does not decrease striated muscle Mg upon prolonged administration [109]. However, mean serum Mg level fell significantly by the twentieth week of a study in which this formulation was given as monotherapy to twelve patients with essential hypertension (*Leary, W. P., Reyes, A. J., van der Byl, K.*: unpublished). This preparation also alters lipid and carbohydrate metabolism [45].

Diuretic formulations that cause important acute hypermagnesiuria, such as chlorthalidone 100 mg and xipamide 10 and

20 mg (Fig. 1) should not be prescribed.

*Minimization of diuretic dose*

Minimization of diuretic dose is the most effective manoeuvre for reducing renal excretions of Mg and K and the deleterious effects of diuretics on lipid and carbohydrate metabolisms [74, 108].

Diuretics are commonly prescribed for patients with oedema or hypertension. Oedema should be treated initially by appropriate attempts at reversal of the primary cause, optimization of dietary salt intake and administration of diuretics at standard doses. Double doses are required at the beginning of treatment if ascites, which impairs the absorption of diuretics, is present. When prolonged diuresis is necessary, the initial dose should be reduced to the minimum compatible with therapeutic objectives, thus limiting urinary potassium and Mg losses. This maintenance dose must be individually titrated but usually lies between one-third and one-half of the dose initially required to control oedema.

Unnecessarily high doses of diuretics are commonly prescribed in the treatment of essential hypertension. This practice should be avoided by applying simple rules to the choice of a suitable therapeutic regime. Loop diuretics are of little practical value in the chronic monotherapeutic treatment of uncomplicated essential hypertension [73—75, 77, 108] since they do not satisfy all the criteria whereby an antihypertensive diuretic is defined. The minimal effective antihypertensive dose of antihypertensive distal tubular diuretics is approximately one-quarter of the standard diuretic dose. Daily doses as small as 12.5 mg hydrochlorothiazide [9] or chlorthalidone [26, 57] or 2.5 mg indapamide [76] should be prescribed in most cases of uncomplicated essential hypertension. At these doses hypermagnesiuria and hyperkaliuria are minimized, while the rate at which blood pressure falls and the final stable value achieved are similar to those recorded in response to standard diuretic doses of the same substances [75].

*Administration of magnesium*

It is important to ensure a diet rich in Mg in patients subjected to chronic diuretic therapy. Diets with at least 300 mg/day are recommended for adult women, 350 mg/day for adult men and 450 mg/day during pregnancy. It has been postulated that these values should be higher, e. g. 450—470 mg/day in adult men [66]. Growing children and persons under stress or with active anabolism should receive at least 5 mg Mg/kg/day. Fruit, vegetables, dairy products and meat contain less than 30 mg of Mg per 100 g, raw flours 100 and bananas 200 mg/100 g.

Magnesium salts may be administered prophylactically in patients on diuretics, at doses of 7.5—15 mmol/day [17] divided between the two principal meals. All magnesium salts currently used prophylactically (chloride, gluconate, citrate, aspartate) are equally well absorbed. All recommended doses apply to a standard adult type of 70 kg body weight.

Arrhythmias developing during treatment with diuretics respond to Mg replacement [21, 23]. The intravenous administration of Mg sulphate normalises intracellular concentrations of both K and Mg in skeletal muscle of patients with hypomagnesaemia and hypokalaemia secondary to prolonged diuresis, whereas simple K replacement does not restore the intracellular levels of either cation to normal [21, 23]. Despite a relatively poor correlation between the intracellular Mg concentrations of skeletal and cardiac muscles, it its likely that these tissues respond similarly to Mg repletion and that the suppression of arrhythmias by Mg is due to a reactivation of $Na^+$, $K^+$-ATPase. Decreases in myocardial Mg and K concentrations are not only caused by the administration of diuretics; digitalis inhibits myocardial $Na^+$, $K^+$-ATPase [1] and myocardial ischaemia has a similar effect on intracellular electrolytes which might contribute to the development of the arrhythmias commonly associated with myocardial infarction [23]. In these circumstances Mg infusion has an antiarrhythmic effect; animal studies have shown that this measure results in repletion of intracellular K and Mg ions in the infarcted area [23].

Intravenous Mg sulphate can be administered as an immediate measure in the treatment of ventricular arrhythmias associated with diuresis, acute myocardial infarction or digitalis therapy [20, 23, 95, 98]. The solution can be given as a bolus of 2.5 g, which usually suppresses arrhythmias within 20—30 seconds, or at a dose of 40 mg/min in a saline infusion. The latter dose is safer in patients with respiratory or cardiac insufficiency and can be continued indefinitely without any detectable rise in the serum Mg level. Alternative parenteral dosage regimes may be used.

During prolonged treatment with diuretics, Mg should be taken orally as a prophylactic measure at a dose of 10—15 mmol (20—30 mEq)/day.This dose should be doubled if evidence of Mg depletion appears. The Mg formulations available for therapy (chloride, aspartate) are equally well absorbed and should be taken in divided doses at meal times.

The only absolute contraindication to Mg administration is an excessive accumulation of the ion which sometimes occurs in

patients with acute or chronic renal insufficiency with a glomerular filtration rate below 30 ml/min, hypothyroidism, viral hepatitis, or Addison's disease and in patients on lithium therapy. Hypermagnesaemia is diagnosed when the plasma level exceeds 1.20 mmol/l, but clinical evidence of Mg overload seldom appears at levels below 2 mmol/l [92]. Initially, nausea and vomiting, rashes, somnolence and reduction of deep tendon reflexes develop. The ECG dispays prolongation of the PR interval and disturbances of intraventricular conduction. When the plasma Mg level reaches 5 mmol/l, skeletal muscles, including respiratory muscles, may become paralysed, with cardiac arrest in diastole likely if the plasma Mg concentration rises to 7.5 mmol/l. Accordingly, plasma levels should be monitored during treatment with Mg supplements. Therapy should be withdrawn and temporary treatment with a loop diuretic instituted if mild hypermagnesaemia develops; if important cardiac complications due to Mg excess are diagnosed, Ca (as calcium gluconate) 100—200 mg should be infused intravenously over 5—10 minutes.

*Low-sodium diet*

Avoidance of significant K losses should be sought during diuretic treatment. The usual procedures to achieve this goal are the prescription of a low-Na diet and the administration of supplementary K or the coprescription of a K-sparing diuretic.

The rate of interchange between Na and K in the distal convoluted tubule depends, amongst other factors, on the amount of Na in the preurine at the interchange level. Restriction of Na intake decreases the filtered Na, preurinary Na and consequently, the urinary K output (Fig. 7). However, if dietary Na restriction is too rigid, the secondary hyperaldosteronism caused by diuretics is reinforced and urinary K losses tend to increase [37, 97] (Fig. 7). For this reason, apparently contradictory experimental and clinical observations exist with respect to the effects of restriction of Na intake on urinary K excretion [37]. In our experience, a daily diet containing 90—150 mmol of Na is compatible with minimal 24-hour urinary K excretion in patients without oedema (hypertensives and controlled patients with cardiac renal or hepatic insufficiency) under chronic diuretic treatment at standard doses. Whenever possible it is desirable to determine the amount of dietary Na that minimizes urinary K excretion during chronic diuretic treatment in each patient. For this purpose, a trial-and-error procedure should be followed in which standardized diets with a known Na content are given and the 24-hour urinary K output evaluated.

*Administration of potassium salts*

The intravenous administration of K salts seems to suppress some serious ventricular arrhythmias provoked by diuretics, but this effect is transient, while the overall myocardial electrolyte derangement remains uncorrected. However, it is advisable to coadminister KCl with intravenous Mg when K in plasma is below 3.5 mmol/l, in order to ensure maximal antiarrhythmic effect. Forty mmol of KCl should be infused in saline over 10 hours. When acidaemia exists, alkaline K salts such as bicarbonate or gluconate should be used [61, 62].

The chronic oral administration of KCl as a prophylactic procedure has no rational basis when the diuretic dose is minimal, Na intake is optimal and Mg intake is supplemented. Oral preparations of KCl should only be given when serum K falls below 3.5 mmol/l. This treatment decreases the K concentration gradient between the cell and the milieu intérieur. Treatment should not be prolonged after the normalization of kalaemia, since it promotes aldosterone secretion (Fig. 7) and may provoke serious side effects, even when slow-release forms are used [47].

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