Interactions between magnesium and drugs in congestive heart failure

A. J. Reyes

Zusammenfassung

Bei kongestiver Herzinsuffizienz sind die Plasma-Konzentrationen an Aldosteron und ANF (atrialer natriuretischer Faktor) erhöht und verursachen jeweils eine erhöhte Mg-Ausscheidung im Urin. Bei entsprechenden Patienten besteht zusätzlich das Risiko eines Mg-Mangels, weil üblicherweise Mg-Zufuhr und Resorption reduziert sind. Schleifendiuretika und solche vom Thiazid-Typ erhöhen die Mg-Ausscheidung über den Urin und können den Mg-Mangel bei kongestiver Herzinsuffizienz verstärken. — Digitalis erhöht das zytosolische Ca^{2+} und ist deshalb potentiell arrhythmogen. Mg-Mangel erhöht die Sensitivität gegenüber Digitalis, wobei kardiale und zentralnervöse Mechanismen involviert sind.

Das Plasma-Mg sollte bei Patienten mit kongestiver Herzinsuffizienz überwacht werden; Magnesium sollte prophylaktisch gegeben werden, wenn die Standarddosen an Diuretika und/oder inotropen Substanzen überschritten werden. Therapiebedürftige kardiale Arrhytmien, die unter der Behandlung kardialer Stauungsinsuffizienzen auftreten, sollten — als erste Maßnahme — mit i. v. Mg^{2+}-Gaben therapiert werden, und zwar unabhängig vom aktuellen Magnesium-Status.

Summary

The plasma concentrations of aldosterone and of atrial natriuretic factor are raised in congestive heart failure; both these deviations elevate magnesiuresis. Patients with congestive heart failure are also at risk of developing Mg^{2+} deficiency because their intake and absorption of Mg^{2+} are usually reduced.

Loop and thiazide-type diuretics augment urinary Mg^{2+} output and may precipitate Mg^{2+} deficiency in congestive heart failure.

Digitalis increases myocardial cytosolic Ca^{2+} and is therefore potentially arrhythmogenic. Magnesium deficiency facilitates digitalis toxicity by mechanisms that take place both in the heart and in the central nervous system.

Plasma Mg^{2+} concentration should be monitored in patients with congestive heart failure. Magnesium supplements should be administered prophylactically in congestive heart failure when standard doses of diuretics and/or inotropics are exceeded.

Cardiac arrhythmias arising during therapy of congestive heart failure and requiring pharmacological handling should be treated with intravenous Mg^{2+} as the first active therapeutic measure, irrespectively of the bodily magnesium status.

Résumé

Les concentrations plasmatiques d'aldosterone et de facteur natriurétique des oreillettes, qui sont augmentées dans l'insuffisance cardiaque congestive, élevent le débit urinaire de Mg^{2+}. L'hypermagnésurie et les abaissements fréquents de l'ingestion et de l'absorption du Mg^{2+}, qui ont lieu pendent l'insuffisance cardiaque congestive, font les malades particulièrement labiles au développement de déficit magnésique.

Les diurétiques d'anse et ceux de type thiazidique accroissent l'excrétion urinaire de Mg^{2+} and peuvent provoquer déficit magnésique dans l'insuffisance cardiaque congestive.

Les digitaliques sont potentiellement arrhythmogeniques parce qu'ils augmentent le Ca^{2+} cytosolique au myocarde; l'intoxication digitalique aussi altère le rhythme cardiaque a travers d'une action toxique sur le systeme nerveux autonome. Ces effets sont facilités par le déficit magnésique.

La magnésémie doit etre mesurée fréquemment chez les malades atteintes d'insuffisance cardiaque congestive. On doit administrer des suppléments de Mg^{2+} par voie orale, à titre prophylactique durant les traitements prolongués avec des doses élevées de diurétiques et d'inotropes.

Les arrhythmies cardiaques qui surgissent pendant le traitement de l'insuffisance cardiaque congestive, et qui méritent des mesures pharmacologiques actives, doivent recevoir thérapeutique magnésique intraveineuse comme traitement d'élection.

Patients suffering from congestive heart failure (CHF) usually require therapeutic regimens including several drugs with which Mg^{2+} interacts. This review will be limited to interactions between Mg^{2+} and the drugs most commonly used for the treatment of CHF. These interactions occur in two different circumstances. Many drugs used in the treatment of CHF may potentially alter the bodily Mg^{2+} turnover at large and therefore the myocardial content of the cation; in addition, the therapeutic use of Mg^{2+} salts is often indispensable in patients receiving pharmacological treatment for CHF, either because of Mg^{2+} deficiency induced by the CHF syndrome and/or by the drugs used to treat it, or because of drug toxicity which is particularly responsive to Mg^{2+} therapy [2, 41, 43].

Interactions between diuretics and magnesium in congestive heart failure

Therapy with diuretics is mandatory in CHF [41, 43]; however, diuretics not only increase the renal excretion of Na^+, but also those of K^+ and Mg^{2+} [2, 41, 43].

Mechanisms of hypermagnesiuresis and magnesium depletion induced by diuretics

Several formulations of loop [21, 31, 50] and distal tubular diuretics [21, 33, 48, 49] have been found to cause hypermagnesiuresis, relative to the somatic Mg^{2+} status, when they are administered acutely to healthy subjects [42, 46] or to patients suffering from CHF [22], although prolonged diuretic therapy does not necessarily cause Mg^{2+} deficiency [42, 46].

The effects of single doses of diverse diuretic formulations on 24-hour urinary electrolyte outputs were studied in biologically equivalent healthy volunteer subjects under strictly controlled conditions. All common-diuretic formulations increased the renal outputs of Cl^-, Na^+ (Tab. 1), fluid and K^+ (Tab. 2) in the first 6 hours after dosing, with respect to excretions after placebo.

All tested diuretic formulations whose main site of renal action lies in the early portion of the distal convoluted tubule (chlorthalidone 100 mg, clopamide 5 mg, hydrochlorothiazide 25 and 50 mg and xipamide 5, 10 and 20 mg) elevated 24-hour urinary Mg^{2+} output significantly with respect to placebo. The formulations muzolimine 30 and 40 mg and torasemide 5 and 10 mg, which mainly act in the loop of Henle, had no significant action on 24-hour urinary Mg^{2+} output, although 40 mg of the loop-diuretic furosemide did (Tab. 3). The amiloride formulations tested did not affect 24-hour urinary Mg^{2+} output in a statistically significant manner, though this K^+-retaining substance showed a weak tendency to retain Mg^{2+} in a dose-dependent fashion (Tab. 3). Amiloride has been found to decrease 24-hour urinary Mg^{2+} output in a similar investigation [21]. It may there-

Tab. 1: Effects of the administration of single doses of various diuretic formulations, at hour 0, on urinary Na^+ output in healthy volunteers. Hour 0 of the experiments corresponds to hour 08.00

Number of subjects	Diuretic and dose (mg)	Post-placebo mean urinary Na^+ output (mmol)			Post-diuretic % change of urinary Na^+ output			Reference
		Hours after dosing			Hours after dosing			
		0–6	6–24	0–24	0–6	6–24	0–24	
13	amiloride 5	36	85	121	55	32	39*	32
13	amiloride 10	36	85	121	71	59	67***	32
9	clopamide 5	52	102	154	129	33	85***	49
14	furosemide 40	49	98	147	204	−24	51***	50
14	hydrochlorothiazide 25	49	98	147	171	43	85***	50
19	hydrochlorothiazide 50	45	132	177	149	30	60***	29
10	muzolimine 20	57	129	186	126	−19	7	31
10	muzolimine 30	57	129	186	154	−20	33**	31
10	muzolimine 40	60	165	225	163	−36	17*	31
14	torasemide 5	49	98	147	92	−4	28	50
14	torasemide 10	49	98	147	161	−42	25	50
13	xipamide 5	43	108	151	95	26	46**	48
13	xipamide 10	43	108	151	191	92	120***	48
13	xipamide 20	43	108	151	140	98	110***	48

Significances of the differences between mean 24-hour post-diuretic and mean 24-hour post-placebo outputs: * $p<0.05$; ** $p<0.01$; *** $p<0.001$

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13	amiloride 10	20	26	46	−30	−35	−33***	32
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14	furosemide 40	17	27	44	52	−20	7	50
14	hydrochlorothiazide 25	17	27	44	59	6	26*	50
19	hydrochlorothiazide 50	17	31	48	65	13	31*	29
10	muzolimine 20	22	32	54	23	−16	0	31
10	muzolimine 30	22	32	54	59	−6	20	31
10	muzolimine 40	17	32	49	106	−22	24*	31
14	torasemide 5	17	27	44	5	−19	−10	50
14	torasemide 10	17	27	44	24	−12	1	50
13	xipamide 5	17	25	42	65	24	40**	48
13	xipamide 10	17	25	42	88	32	55**	48
13	xipamide 20	17	25	42	71	84	79***	48

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13	amiloride 10	1.0	3.1	4.1	−14	−5	−7	32
9	clopamide 5	1.1	3.8	4.9	58	19	27**	49
14	furosemide 40	1.0	2.8	3.8	96	27	45*	50
14	hydrochlorothiazide 25	1.0	2.8	3.8	76	87	84***	50
19	hydrochlorothiazide 50	1.0	3.7	4.7	57	15	24*	29
10	muzolimine 20	1.3	3.4	4.7	34	−21	−6	31
10	muzolimine 30	1.3	3.4	4.7	52	−8	9	31
10	muzolimine 40	1.2	3.6	4.8	84	−15	11	31
14	torasemide 5	1.0	2.8	3.8	67	−8	12	50
14	torasemide 10	1.0	2.8	3.8	93	−30	3	50
13	xipamide 5	1.0	3.0	4.0	21	30	28**	48
13	xipamide 10	1.0	3.0	4.0	47	51	50***	48
13	xipamide 20	1.0	3.0	4.0	22	47	40***	48

Significances of the differences between mean 24-hour post-diuretic and mean 24-hour post-placebo outputs: * $p<0.05$; ** $p<0.01$; *** $p<0.001$

fore be concluded that formulations of furosemide and of early distal tubular diuretics in use cause hypermagnesiuresis in the 24-hour period that follows administration, and that amiloride would cause renal retention of Mg^{2+}, but to a much lesser extent than it retains K^+.

The 24-hour urinary Mg^{2+} and K^+ outputs after dosing with the formulations of common diuretics studied (Tab. 2 and 3) were related to diuretic-induced natriureses, as shown by the rather unimpressive differences between any two mean 24-hour urinary Mg^{2+}/Na^+ or K^+/Na^+ ratios after diuretics; urinary Mg^{2+}/Na^+ varied more between experiments than K^+/Na^+ did, although it occurred both before and after medication (Tab. 4).

Tab. 4: Effects of the administration of single doses of various diuretic formulations on the 24-hour post-dosing K^+/Na^+ and Mg^{2+}/Na^+ ratios

Number of subjects	Diuretic and dose (mg)	Mean 24-hour urinary K^+/Na^+ ratio (mmol/mmol)		Mean 24-hour urinary Mg^{2+}/Na^+ ratio (cmmol/mmol)		Reference
		placebo	diuretic	placebo	diuretic	
13	amiloride 5	0.38	0.19	3.36	2.38	32
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9	clopamide 5	0.40	0.27	3.23	2.22	49
14	furosemide 40	0.30	0.21	2.61	2.50	50
14	hydrochlorothiazide 25	0.30	0.20	2.61	2.58	50
19	hydrochlorothiazide 50	0.28	0.22	2.68	2.08	29
10	muzolimine 20	0.29	0.27	2.53	2.21	31
10	muzolimine 30	0.29	0.26	2.53	2.06	31
10	muzolimine 40	0.22	0.23	2.13	2.01	31
14	torasemide 5	0.30	0.21	2.61	2.28	50
14	torasemide 10	0.30	0.24	2.61	2.12	50
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13	xipamide 10	0.28	0.20	2.67	1.82	48
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Loop diuretics

Loop diuretics block the transparietal reabsorption of Mg^{2+} at the thick ascending limb of the loop of Henle, where most filtered Mg^{2+} is reabsorbed, and thus augment urinary Mg^{2+} excretion [42, 46].

The mechanism whereby muzolimine 20, 30 and 40 mg and torasemide 5 and 10 mg did not increase 24-hour urinary Mg^{2+} output significantly in normal volunteers (Tab. 3), and the possible processes involved deserve analysis. These lacks of effect were principally due to undershoots — i. e. reductions below postplacebo values — of urinary Mg^{2+} excretions which followed the significant drug-induced increases in excretion occurring immediately (0–6 hours) after dosing (Tab. 3). These undershoots, which took place in the 6–24-hour period after drug administration (Tab. 3), were also ostensible for Na^+ (Tab. 1, Fig. 1) and for K^+ (Tab. 2) urinary flows, and their existence has been confirmed in healthy volunteers [22] and in mild CHF [21], after administration of single doses of loop diuretics, by investigators other than this author and his coworkers. The mechanism of these undershoots has not been studied. It may be speculated that they are principally caused by a reduction in glomerular filtration that occurs as a consequence of hypovolaemia, and subsequently reduced renal plasma flow, after the marked initial excretory effect of loop

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and absorption in the two groups of subjects. Additionally, CHF per se places patients at risk of developing hypermagnesiuresis, principally through a rise in aldosteronaemia which would alter significantly the nephronal parietal transport of Mg^{2+}; thus the weak Mg^{2+}-retaining effect of amiloride could be more important in CHF patients than in healthy subjects.

Amiloride apparently retains Mg^{2+} by a direct nephronal action whereby the reabsorption of the cation at the early collecting duct is reduced. However, amiloride, like the thiazides, decreases urinary Ca^{2+} excretion by promoting its reabsorption from the preurine in the early distal convoluted tubule [6]; the hypercalcaemia and the reduction in plasma PTH that ensue would tend to increase magnesiuresis [42, 46].

Reduction of plasma and cellular magnesium caused by diuretics in congestive heart failure

In several studies in which patients suffering from CHF had been receiving diuretics for prolonged periods the concentration of Mg^{2+} in plasma [58, 66], skeletal muscle [9, 11], erythrocytes [34] and leucocytes [66] was found to be reduced below its inferior normal limit, on average and/or in many individual patients. A prospective study in CHF found that treatment with furosemide 40 to 80 $mg \cdot day^{-1}$ is capable of reducing the intralymphocytic Mg^{2+} content in less than one week [54].

No data are available on the effects of chronic diuretic administration on total body Mg^{2+} or on the myocardial Mg^{2+} content in man.

Congestive heart failure courses with hyperaldosteronaemia (relative to plasma Cl^-, Na^+, K^+ and Mg^{2+} concentrations) [40, 43], with an increase in circulating atrial natriuretic factor [3, 59], and, in about 50 percent of cases, with a rise in circulating arginine-vasopressin [40] (Fig. 3). Aldosterone [19, 49] increases renal Mg^{2+} output in man [19, 33, 42, 49], and atrial natriuretic factor (ANF) has been found to increase magnesiuresis in the rat [25] and in man [65]. Diuretics elevate aldosteronaemia further

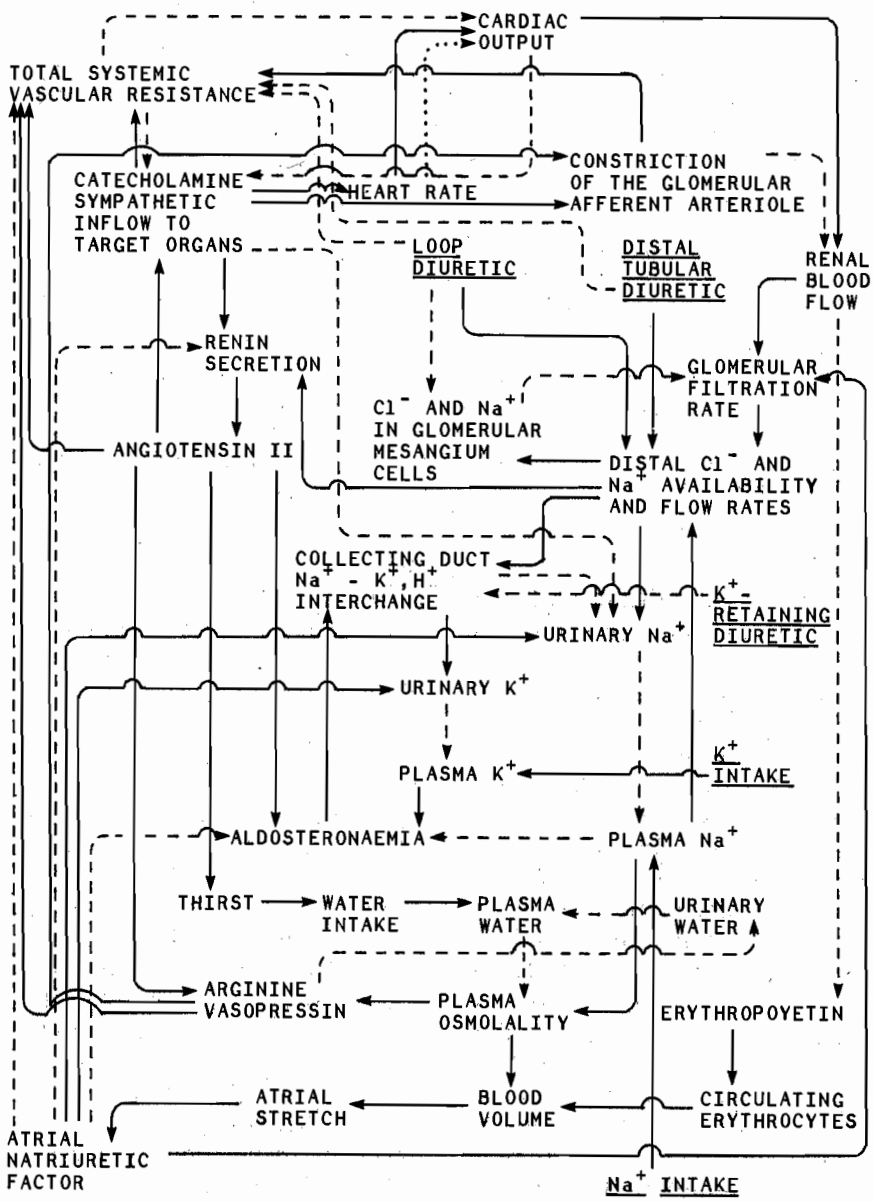

Fig. 3: Causative diagram of some of the processes involved in water, Na^+ and K^+ turnovers in congestive heart failure. External dietary and pharmacological factors that may act upon the natural system variables are underlined. Each arrow depicts the direction of the changes that the departing factor or increases in the departing variable induce in the receiving variable: continuous arrows represent augmentations, dashed arrows represent diminutions, and the dotted arrow represents diminutions elicited by extreme increases in the departing variable. The absence of or an even number of dashed arrows connecting any factor to any variable or any two variables by any determined pathway indicates that the factor or increases in the departing variable cause increases in the receiving variable by that specific route; and odd number of dashed arrows in analogous conditions indicates that the factor or increases in the departing variable cause decreases in the receiving variable. Adapted from [43], by courtesy of Elsevier Science Publishing Co., Inc.

in CHF [41, 43], principally through their Cl^- and Na^+-excretory effect, and thus enhance the already augmented renal excretion of Mg^{2+}. Diuretics abate the plasma concentration of ANF [3]; however the decrease in renal Mg^{2+} output that could result from this shift would be outweighed by the elevation in aldosteronaemia that would result from the fall in plasma ANF [28]. A schematic representation of these and other hormonal mechanisms positively or possibly involved in diuretic-induced hypermagnesiuresis in CHF is depicted in Fig. 4.

Tab. 6: Effects of the administration of single doses of various formulations of angiotensin-I converting enzyme inhibitors on 24-hour urinary Na^+ and Mg^{2+} outputs in healthy volunteers

Number of subjects	Angiotensin-I converting enzyme inhibitor and dose (mg)	Control mean 24-h urinary electrolyte outputs (mmol)		Post-diuretic % change of mean 24-h urinary outputs		Reference
		Na^+	Mg^{2+}	Na^+	Mg^{2+}	
13	Captopril 100	146	4.2	−3	18**	33
11	Perindopril 4	162	4.9	25	−14	(a)
11	Perindopril 8	174	4.9	34*	0	(a)
11	Perindopril 16	149	4.9	15	−6	(a)

Significances of the differences between mean 24-hour post-angiotensin-I converting enzyme inhibitor and mean 24-hour post-placebo outputs: * $p<0.05$; ** $p<0.01$. (a) *A. J. Reyes, W. P. Leary* and *K. van der Byl:* unpublished data

Interactions between digitalis and magnesium in congestive heart failure

Cardiac glycosides increase contractility in the normal and in the failing heart. Many recent reviews deal with the present-day clinical use of these substances and with the mechanisms of their therapeutic action and toxicity [1, 4, 12, 23, 64]. Consecrated medical experience indicates that digitalis should always be prescribed, together with diuretics, in CHF, unless contraindications for the use of cardiac glycosides exist.

Mechanisms of the therapeutic and toxic actions of digitalis

Positive inotropic effect of digitalis

Digitalis binds to sarcolemmal Mg^{2+}-dependent Na^+, K^+ ATPase [1, 12, 23], both in the myocardium and in vascular smooth muscle. The union of digitalis to Na^+, K^+ ATPase inhibits the activity of this enzyme [1]. The consequences of this inhibition are a decrease in sarcoplasmic K^+ and an increase in sarcoplasmic Na^+, because the active pumping of these cations across the sarcolemma which takes place during the majority of the cardiac cycle, i. e. when the membrane potential is above the electrochemical potential of K^+ and below that of Na^+, becomes impaired. The accumulation of Na^+ within the sarcomere is followed by an augmented activity of the Na^+-extruding Na^+/Ca^{2+} exchanger and by a lowered activity of its Na^+-incorporating counterpart [37] (Fig. 5). These shifts are partly successful in reducing the augmented intracellular Na^+ and, at the same time, they increase the level of free cytosolic Ca^{2+} that replenishes the stores of this cation in the sarcoplasmic reticulum after systole, thus allowing a greater Ca^{2+} release from the sarcoplasmic reticulum induced by Ca^{2+} entering the myocyte through the sarcolemma in the following cardiac cycle (Fig. 5) and consequently improving myocardial contractility. The increases in intracellular Na^+ and in pericellular K^+ tend to augment the activity of the Na^+, K^+ ATPase, but they can not level off the inhibiting effect of digitalis (Fig. 5). An exaggerated increase in cytosolic Ca^{2+} during diastole eventually results from the fact that the increased cytosolic Ca^{2+} can not be entirely incorporated by the sarcoplasmic reticulum because of the limited storing capacity of this compartment and because of the malfunction that exists in CHF in the Mg^{2+}-dependent Ca^{2+} ATPase [27] that pumps Ca^{2+} into the sarcoplasmic reticulum [40, 56]. The excess in cytosolic Ca^{2+} can not be disposed of by the Na^+/Ca^{2+} exchanger because the changes in the intracellular Na^+ concentration predominate as determinants of the function of this system. The Mg^{2+}-dependent sarcolemmal Ca^{2+} ATPase would exert a poor action in ridding the cytosol of Ca^{2+} primarily because the transporting capacity of this enzyme is limited [27].

The increase in cytosolic Ca^{2+} caused by digitalis augments the sarcolemmal conductance for Na^+ and for K^+; both cations cross the plasma membrane passively driven by their electrochemical gradients, thus further increasing intracellular Na^+ and reducing intracellular K^+ (Fig. 5). This positive feedback of cytosolic Na^+ concentration further deviates the function of the Na^+/Ca^{2+} exchanger towards a Na^+-extruding pattern and potentiates the increase in cytosolic Ca^{2+} (Fig. 5).

The rise in cytosolic Ca^{2+} caused by digitalis tends to overload the mitochondria with this cation, a fact which may result in a deterioration in the function of the

organelles and thus in an impairment in ATP generation [16]. This reduction in substrate availability for the sarcolemmal Na^+, K^+ ATPase further decreases the activity of the enzyme; the activities of sarcolemmal and sarcoplasmic Ca^{2+} ATPases are also reduced and cytosolic Ca^{2+} becomes further increased. All these mechanisms, which stem from the Ca^{2+}-induced impairment of mitochondrial function, become particularly relevant in digitalis intoxication.

Digitalis not only acts at the heart level. Plasma digitalis concentrations within the therapeutic range increase the parasympathetic drive by a direct action in the central nervous system and indirectly by peripheral effects [64], such as an increase in the activity of arterial baroreceptors, directly effected by digitalis and which also result from the increase in cardiac output and perhaps from a digitalis-induced rise in total systemic vascular resistance (Fig. 5). The elevation in parasympathetic tone directly decreases cAMP synthesis in the heart, reduces the sympathetic inflow to myocardial beta-adrenergic receptors, and deactivates the myocardial protein kinases which influence Ca^{2+} ATPases positively (Fig. 5). The overall result of these parasympathetic actions is a decrease in myocardial contractility, secondary to a relative reduction in the phasic — systolic — availability of cytosolic Ca^{2+}, which is caused by a lowered capacity of the Ca^{2+} ATPase at the sarcoplasmic reticulum to incorporate the cation into the compartment. The increase in parasympathetic activity is accompanied by a decrease in sympathetic outflow caused by the rise in cardiac output (Fig. 5). These indirectly-acting negative inotropic effects of digitalis counter its direct positive action on myocardial contractility to some extent. The activation of vagal drive is responsible for the negative, chronotropic and dromotropic effects of digitalis, which may be clinically ostensible at therapeutic plasma levels of the drug.

Digitalis intoxication

Digitalis intoxication has been subject to recent reviews [4, 12]. Digitalis toxicity results from an absolute increase in plasma digitalis concentration or from an intensification of digitalis action at therapeutic plasma levels of the compound. Absolute increases are caused by excessive dosing or, less frequently, by an impairment in excretion, as occurs in renal insufficiency. The action of digitalis is intensified by a greater binding of the cardiac glycoside to the plasma membrane Na^+, K^+ ATPase in the heart [1,

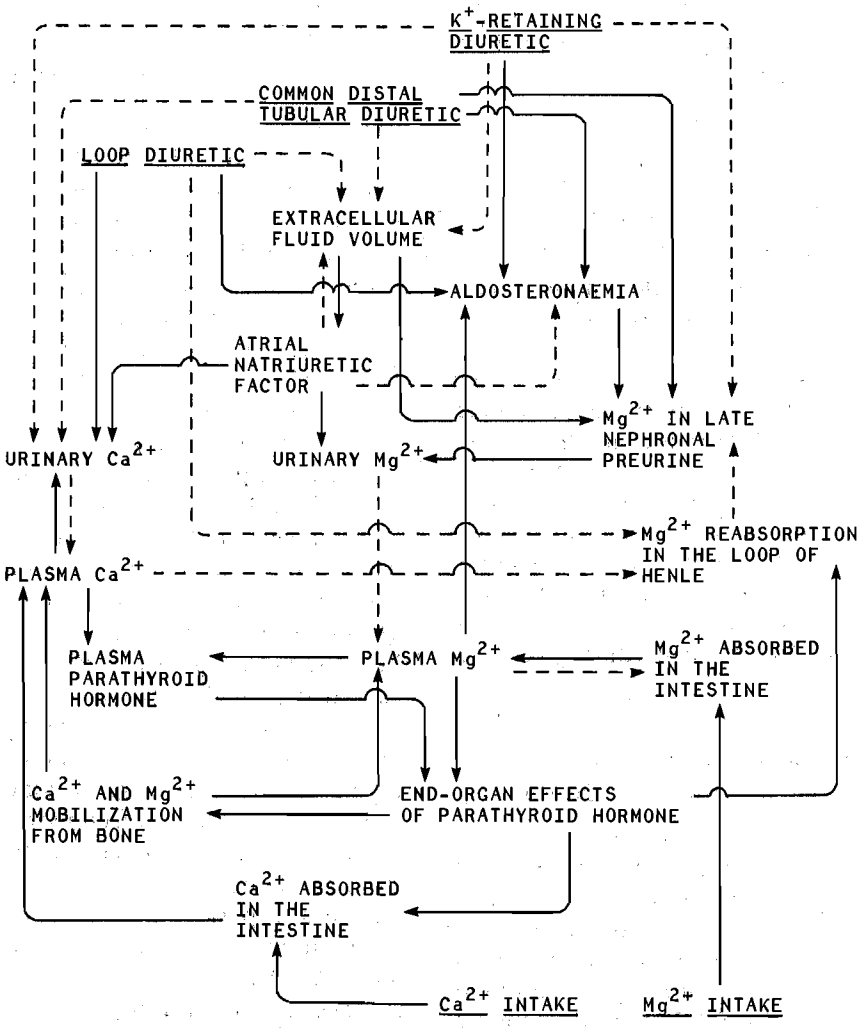

Fig. 4: Causative diagram of some of the processes involved in Mg^{2+} turnover in congestive heart failure. External dietary and pharmacological factors that may act upon the natural system variables are underlined. Each arrow depicts the sign of the changes that the departing factor or increases in the departing variable induce in the receiving variable: continuous arrows represent augmentations and dashed arrows represent diminutions. The absence of or an even number of dashed arrows connecting any factor to any variable or any two variables by any determined pathway indicates that the factor or increases in the departing variable cause increases in the receiving variable by that specific route: an odd number of dashed arrows in analogous conditions indicates that the factor or increases in the departing variable cause decreases in the receiving variable. Adapted from [43], by courtesy of Elsevier Science Publishing Co., Inc.

52] and in the central nervous system [62], which are respectively facilitated by low plasma K^+ and low plasma Mg^{2+}; both serum cation concentrations are usually abated by chronic diuretic therapy, thus making digitalis intoxication more likely during concomitant diuretic therapy. In addition, some loop diuretics are capable of decreasing the activity of the Na^+, K^+ ATPase [26], thus adding to the effect of digitalis on the myocardium.

Toxic plasma levels of digitalis or increased effects of the glycoside on the central nervous system stimulate the central sympathetic activity (Fig. 5) [62], a fact which further increases free cytosolic Ca^{2+} throughout the cardiac cycle. In addition, all the effects of subtoxic plasma levels of digitalis are maintained and increased, i.e., parasympathetic output increases more, and existing shifts in the myocardial concentrations of Na^+, K^+ and free cytosolic Ca^{2+} during diastole become amplified (Fig. 5). The toxic increase in cytosolic Ca^{2+} during diastole increases cardiac excitability [4, 12], causing delayed depolarising afterpotentials that express themselves as ectopic electrical activity [4, 60].

Elevated cytosolic Ca^{2+} also causes slow action potentials that decrease conduction, thus paving the way to reentry arrhythmias [4, 60]. The decrease in cellular K^+ concentration and the accompanying relative increase in this variable at the outer side of the sarcolemma caused by digitalis also raise cardiac excitability. Another factor that increases myocardial excitability is the myocardial hypoxia that occurs because of cardiac hypertrophy and/or dilatation, that may also be due to concomitant coronary artery disease, and

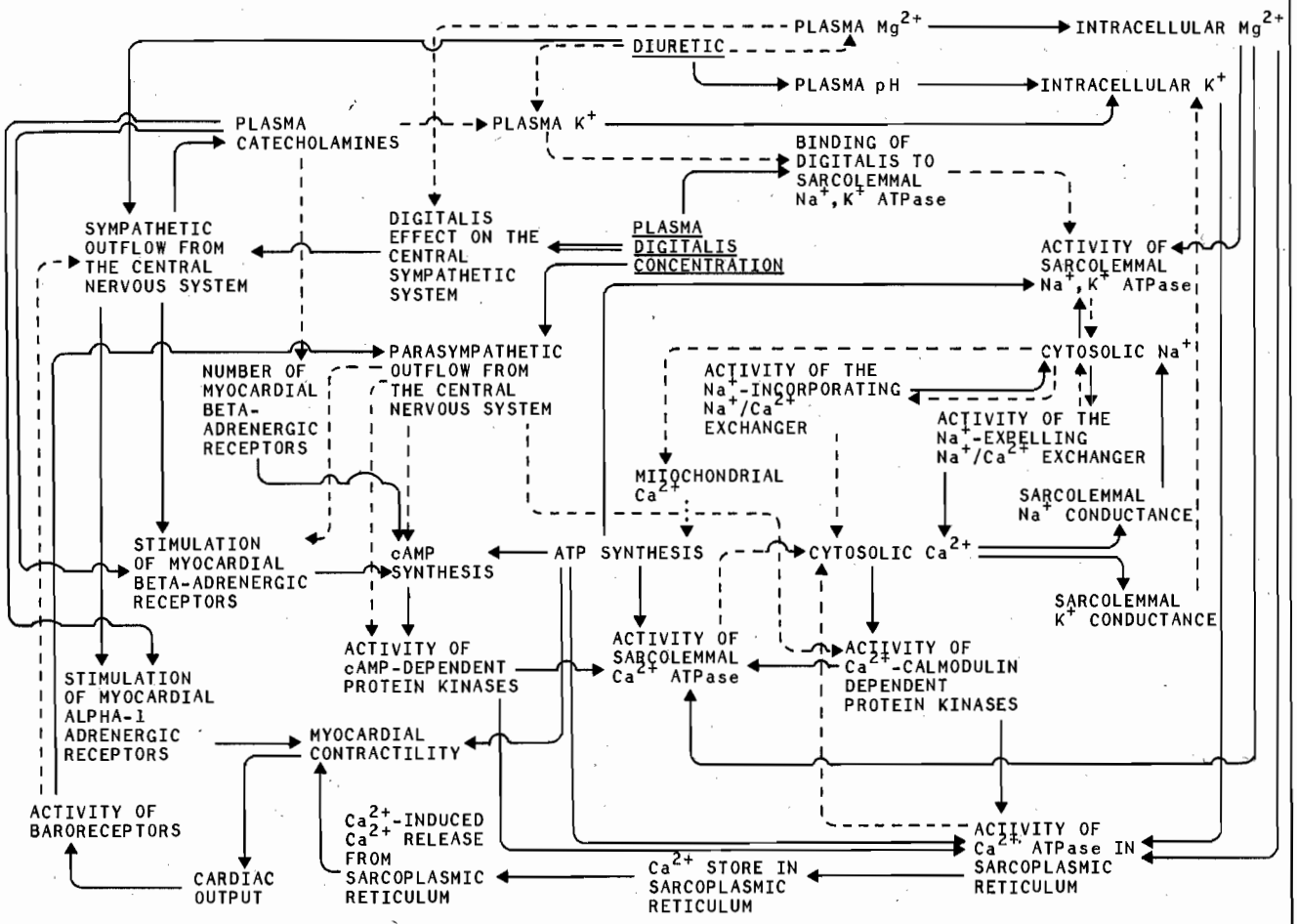

Fig. 5: Causative diagram of some of the processes involved in the effects of digitalis and diuretics on myocardial Na^+, K^+, Mg^{2+} and Ca^{2+}. A pharmacological and a pharmacologically-induced factor that may act upon the natural system variables are underlined. Each arrow depicts the direction of the changes that the departing factor or increases in the departing variable induce in the receiving variable: continuous arrows represent augmentations, dashed arrows represent diminutions, and the double continuous arrow represents augmentations elicited by extreme increases in the departing factor. The absence of or an even number of dashed arrows connecting any factor to any variable or any two variables by any determined pathway indicates that the factor or increases in the departing variable cause increases in the receiving variable by that specific route; an odd number of dashed arrows in analogous conditions indicates that the factor or increases in the departing variable cause decreases in the receiving variable

that is always aggravated by digitalis since the increase in contractility induced by the glycoside augments the myocardial oxygen demand.
Paradoxically, when the therapeutic effect of digitalis gives rise to its toxic actions, there is a decrease in myocardial contractility. The origin of this reduction in inotropism is not clear. In addition to incidents that clearly reduce inotropism, such as arrhythmias, the excessive amount of Ca^{2+} in the sarcomere would affect mitochondrial function and ATP synthesis. Magnesium deficiency, which also raises mitochondrial Ca^{2+} unduly [16, 20], potentiates the decrease in inotropism caused by digitalis [63].

Magnesium deficiency and digitalis toxicity

Digitalis increases magnesiuresis [35], perhaps through its effects on renal Na^+, K^+ ATPases involved in the handling of Mg^{2+} by the nephron. Thus, digitalis constitutes a contributory factor to the genesis of Mg^{2+} deficiency in CHF.
Magnesium deficiency of any origin has an overall effect on myocardial biochemistry which is qualitatively similar to that of digitalis, and hypomagnesaemia potentiates digitalis toxicity [63]. Magnesium deficiency increases free cytosolic Ca^{2+}, decreases intracellular K^+, augments intracellular Na^+ and causes a deterioration in mitochondrial function by allowing an overload of the organelles with Ca^{2+} [16, 20]. The intimate mechanisms whereby these effects of Mg^{2+} deficiency are orchestrated are however controversial. The most accepted view is that the prime effect of Mg^{2+} deficiency is a less opposed passage of Ca^{2+} into the cytosol from the extracellular space; further processes linked to the augmentation in cytosolic Ca^{2+} would result from the decrease in the activities of the Mg^{2+}-dependent Ca^{2+} ATPases that, acting both at the sarcolemma and at the membrane of the sarcoplasmic reticulum, contribute to clear Ca^{2+} from the cytosol. The elevations in Na^+ and K^+ conductances secondary to the rise in free cytosolic Ca^{2+} could explain the shifts in the concentrations of these cations in the sarcomere in Mg^{2+} deficiency. However, a reduction in the activity of sarcolemmal Na^+, K^+ ATPase, stemming from the lack of necessary Mg^{2+} for the correct function of the enzyme system, may not be discarded as at least a contributory mechanism to the cardiac ionic derangement that occurs in bodily Mg^{2+} depletion.
Whatever the ultimate mechanism of the effects of Mg^{2+} deficiency on the myocardial cationic pattern might be, the final effect is an addition, if not a supra-addition, between the toxic actions of digitalis on the heart and those of Mg^{2+} deficiency [36, 63]. Furthermore, experimental findings are clear in that Mg^{2+} deficiency augments the toxic effects of digitalis on the central nervous system [62].

Therapeutic effect of magnesium in digitalis intoxication

Clinical evidence

Digitalis intoxication is usually treated simply by withdrawal of the causative agent, and this is the correct clinical approach when the degree of intoxication is mild, no life-endagering cardiac arrhythmias exist, and the patient may be followed in an intensive care unit. The absence of any of these conditions imposes a demand for active treatment.
Many therapies have been tried and are used in digitalis intoxication complicated by cardiac arrhythmias which require active treatment, from parenteral infusions of K^+ to injection of anti-digoxin antibodies. None of these therapies has however proven to be as effective and as innocuous as Mg^{2+} administration [8, 17, 38, 52]. Moreover, Mg^{2+} administration stands as the most successful monotherapy of cardiac arrhythmias caused by digitalis, irrespective of the plasma Mg^{2+} concentration that antecedes the infusion of the cation.

Mechanisms of the action of magnesium in digitalis intoxication

The mechanisms whereby Mg^{2+} therapy suppresses digitalis-induced cardiac arrhythmias have not been unequivocally elucidated; the possible intervention of various processes (Fig. 5) has been postulated or negated in the evaluations of several experimental and clinical results [24, 52]. The bodily statuses of Mg^{2+} and K^+, other somatic variables such as acid-base balance, and the cardiac pathologies upon which digitalis-induced cardiotoxicity develops, obviously originate diverse predominances within the set of the likely mechanisms whereby Mg^{2+} exerts its beneficial effect in digitalis-induced heart rhythm disturbances.
Magnesium would counter digitalis toxicity by acting in the heart, and perhaps also in the central nervous system. At the cardiac biochemical level, Mg^{2+} could partly restore the activity of sarcolemmal Na^+, K^+ ATPase, and thereby directly increase the myocardial content of K^+ [11] and indirectly reduce free cytosolic Ca^{2+}; the prevailing view is notwithstanding that Mg^{2+} acts by reducing the concentration of cytosolic Ca^{2+} in the sarcomere during diastole, principally by blocking Ca^{2+} entry through the voltage-operated

channels during depolarization, and/or by facilitating Ca^{2+} extrusion from the cytosol after systole through activation of the Ca^{2+} ATPases situated in the membrane of the sarcoplasmic reticulum and in the plasma membrane [24]. Additionally, Mg^{2+} could abate the binding of digitalis to the sarcolemma, particularly when administered to cases with Mg^{2+} deficiency [52].

The cardiac electrophysiological mechanisms of the suppressive effect of Mg^{2+} on digitalis-induced arrhythmias mainly consist in the reduction in the frequency, or in the elimination, of delayed depolarizing afterpotentials and of slow action potentials. These effects imply that the pathophysiologically increased electrical excitability of the heart and the pathological conductions that make possible the reentry of arrhythmogenic impulses are diminished or abolished [60]. Additionally, Mg^{2+} elevates the duration of the absolute refractory period, reduces that of the relative refractory period and decreases the supra-normal cardiac excitability that follows the repolarization of the heart for a short lapse [7]; thus, Mg^{2+} decreases the likelihood of occurrence of perilous R-on-T and early-after-T ectopics. Magnesium ion also diminishes the threshold for the development of ventricular fibrillation.

Interactions between angiotensin-I converting enzyme inhibitors and magnesium in congestive heart failure

When CHF patients treated with cardiac glycosides and diuretics are in a stable, although not compensated, clinical condition, superimposed treatment with angiotensin-I converting enzyme (ACE) inhibitors improves the functional class of many patients.

Angiotensin-I converting enzyme inhibitors are facultative diuretics [45] whose natriuretic action becomes overt when the renin-angiotensin-aldosterone system is mildly or moderately activated by heart failure, diuretic therapy and/or a low Na^+ intake.

Acute randomized and double-blind experiments carried out under strictly controlled conditions, in which healthy subjects received a daily Na^+ diet of around 160 mmol, showed that a single dose of captopril 100 mg exerts no effect on the 24-hour renal outputs of Na^+ and K^+ when there is no cause for the renin-angiotensin-aldosterone system to be activated [33]. However, captopril increased 24-hour post-dosing magnesiuresis significantly. When single doses of hydrochlorothiazide 25 mg alone and a combination of captopril 100 mg and hydrochlorothiazide 25 mg were separately administered to the same volunteers, captopril was found to increase the hydrochlorothiazide-induced 24-hour renal outputs of Na^+ and Cl^- significantly, to blunt hydrochlorothiazide-induced hyperkaliuresis and to diminish hydrochlorothiazide-dependent magnesiuresis, though the combination still had a magnesiuretic effect by comparison with the excretion of Mg^{2+} after placebo [33]. The natriuretic, chloriuretic and relative anti-magnesiuretic effects of the ACE inhibitor were only exposed when the diuretic activated the renin-angiotensin-aldosterone system. Captopril possibly causes hypermagnesiuresis by a direct action on the kidney, but it would tend to retain Mg^{2+} via the decrease in plasma aldosterone it elicits under appropriate functional conditions for this interaction to become overt. When various single doses of the non-sulphydryl ACE inhibitor perindopril were given to healthy volunteers, following an analogous protocol to that used for studying the effects of captopril (*A. J. Reyes, W. P. Leary* and *K. van der Byl,* unpublished), no significant increase in the 24-hour urinary Mg^{2+} output that followed medication occurred (Tab. 6).

This contrast with captopril could be due to different direct pharmacological actions of the two ACE inhibitors on the renal handling of Mg^{2+}, perhaps stemming from the presence in the captopril molecule, or from the absence in perindopril, of a sulphydryl group. If perindopril tended to retain Mg^{2+} via the reduction it causes in aldosteronaemia, such tendency would express itself as an ostensible effect when the renin-angiotensin-aldosterone axis is activated.

The influence of ACE inhibitors on urinary Mg^{2+} excretion and somatic Mg^{2+} turnover must be studied in patients with CHF to determine which of these drugs are magnesiuretic per se, and to define the extent to which ACE inhibitors could be capable of counteracting diuretic-induced hypermagnesiuresis and under which pathophysiological conditions. In an open study, the addition of captopril to the therapeutic regimen of patients with severe CHF, who were not compensated by digitalis and extremely high doses of diuretics, was followed by a high mortality rate within a relatively short period [61]. The possibility should be considered that captopril could have contributed to these deaths by affecting Mg^{2+} turnover, although the very elevated doses of diuretics used could also be incriminated.

Diagnosis of magnesium deficiency during treatment of congestive heart failure

The clinical aspects of Mg^{2+} deficiency (somatic depletion of Mg^{2+}) are extensively considered in various recent reviews and monographs [14, 42, 46, 53]; the present consideration of the topic will be limited to the CHF patient who is being treated with diuretics and digitalis.

The existence of Mg^{2+} deficiency should be suspected in all cases of CHF, especially when diuretic treatment has been prolonged or carried out at high doses, or when any factor other than the CHF-induced hormonal derangements (Fig. 3 and 4) and diuretic treatment has existed or exists that may cause Mg^{2+} deficiency per se or that may precipitate, aggravate or perpetuate this condition [42]. Congestive heart failure, especially in its advanced stages, inevitably conveys some of these aggregated factors: patients generally eat little food, the intestinal absorption of Mg^{2+} is habitually impaired by the alterations in the motility of the digestive tract, in the paradigestive exocrine secretions and in the enteric circulation that occur in CHF; furthermore, iatrogenically-determined disorders of the gastrointestinal tract motility, that cause enteral losses of Mg^{2+}, occur frequently. Many of these factors may also provoke somatic depletion of K^+ or contribute to its development.

The early clinical diagnosis of Mg^{2+} deficiency in patients suffering from CHF and treated with diuretics is particularly difficult since signs and symptoms of somatic Mg^{2+} depletion are not specific; these clinical indicators, which include anorexia, apathy, muscular weakness and fatigue may also be due to other electrolyte derangements arising from the CHF syndrome (Fig. 3 and 4) and/or from diuretic therapy. Chvostek's and Trousseau's signs may be present as more characteristic features, although they are not specific either because they may be due to hypocalcaemia secondary to prolonged therapy with loop diuretics. In many cases the first clinically ostensible expression of Mg^{2+} deficiency is a cardiac supraventricular or ventricular arrhythmia; heart rhythm disturbances develop at less severe Mg^{2+} deficiency levels in damaged myocardia and in CHF, and Mg^{2+} deficiency decreases the threshold, in terms of digitalis plasma concentration, at which cardiac glycosides induce heart rhythm disturbances. Electrocardiographic features of Mg^{2+} deficiency, including prolongation of the PQ, QTc and QUc intervals and flattening of the T waves, also lack specificity, and in patients suffering from CHF they are commonly caused by the underlying myocardial disease, by myocardial hypertrophy or dilatation, and/or by digitalis therapy. Clinically overt Mg^{2+} deficiency may give rise to excitation and sometimes to delirium or coma. Other signs include peripheral tremor — involving muscles of the tongue, face and limbs — ataxia, vertigo, lateral and vertical nystagmus, tetany and convulsions. Myoclonia and spontaneous carpopedal spasms occasionally occur. Muscular derangements of the inferior portion of the oesophagus lead to dysphagia, a symptom which may also be accentuated by important cardiac enlargement. Advanced stages of Mg^{2+} deficiency may be clinically confused with hypocalcaemic tetany.

Microcytic anaemia with decreased erythrocytic half life, reticulocytosis and spherocytosis may be present in blood. This haematological picture sometimes occurs in CHF as a consequence of impaired iron absorption in the digestive tract.

Metabolic alkalosis occurs, especially when patients receive loop or distal tubular diuretics, all of which promote H^+ renal excretion; when patients are treated with K^+-retaining diuretics, which also retain H^+, Mg^{2+} deficiency may be accompanied by a normal plasma pH value or even by acidosis, mainly when CHF is severely decompensated. Total body K^+ is decreased. Hypokalaemia is practically always present in Mg^{2+} deficiency in CHF in patients treated with diuretics [65], even in some cases in whom K^+ supplements or K^+-retaining diuretics are being coadministered (*A. J. Reyes,* unpublished). Hypokalaemia usually resists supplementation therapy in Mg^{2+} deficiency unless Mg^{2+} is supplemented too [66]. Hypocalcaemia is almost a constant feature of Mg^{2+} deficiency in general and especially in loop-diuretic-induced Mg^{2+} deficiency, since furosemide-like substances cause hypercalciuresis. Magnesium deficiency secondary to treatment with early distal tubular diuretics may course with a normal plasma Ca^{2+} concentration, insofar as these diuretics diminish calciuresis. Total plasma lipids are usually elevated; most frequently LDL cholesterol is augmented and sometimes the HDL cholesterol is augmented and sometimes the HDL cholesterol fraction is decreased.

No routine procedure exists for the evaluation of total bodily Mg^{2+} levels. Magnesium deficiency is conventionally diagnosed when the total plasma Mg^{2+} concentration is below 0.70 $mmol.L^{-1}$ (1.40 $mEq.L^{-1}$), although more stringent criteria have also been used [65]. The upper limit of normality is 1.10 $mmol.L^{-1}$ (2.20 $mEq.L^{-1}$). Since about 25 % of total Mg^{2+} in plasma is bound to albumin and 8 % to globulins, plasma protein concentrations have to be

measured when total plasma Mg^{2+} is evaluated, and appropriate corrections have to be made for dysproteinaemia when pertinent. This is particularly important in patients with advanced CHF, in whom consentaneous deterioration of hepatic function usually results in hypoalbuminaemia. Although plasma Mg^{2+} concentration is always low in clinically ostensible Mg^{2+} deficiency and is often low in clinically covert Mg^{2+} depletion, a normal serum Mg^{2+} level does not exclude somatic Mg^{2+} deficiency, since Mg^{2+} is mobilized from its store in bone into plasma in the early stages of somatic Mg^{2+} depletion. Serial determinations of plasma Mg^{2+} concentration during treatment with diuretics may show fluctuations indicating incipient Mg^{2+} deficiency.

The concentration of Mg^{2+} in skeletal muscle has been used to estimate the ion content in soft tissue [9–11], but proof has never been afforded that it could bear any definite relationship to myocardial Mg^{2+}; when deficiency develops Mg^{2+} would be lost from skeletal muscle more readily than from the heart. Measurement of the Mg^{2+} concentration in various blood cells, such as erythrocytes [34, 57] and leucocytes [54, 55], has been used as means for estimating the somatic status of Mg^{2+}. Lymphocytes [18, 54] are much in use for this purpose. Magnesium concentrations in erythrocytes and lymphocytes correlate linearly, although lymphocytic and skeletal muscle Mg^{2+} concentrations do not correlate linearly in patients treated with diuretics [10]. The concentrations of Mg^{2+} in lymphocytes and in the myocardium correlate linearly in the rat [15]; however, the extent to which intralymphocytic Mg^{2+} concentration might correlate with the intramyocardial concentration of the cation in man, under different metabolic and therapeutic conditions, remains to be investigated.

Prophylaxis and therapy of magnesium deficiency during treatment of congestive heart failure

Any factor other than the CHF syndrome and the drugs used for its treatment likely to induce Mg^{2+} deficiency, should be corrected whenever possible.

Diet

Magnesium diet

It is important to ensure a diet rich in Mg^{2+} in CHF patients in general; this requirement becomes more stringent when patients undergo chronic diuretic therapy and/or receive inotropic drugs. In persons who are not being treated with diuretics and/or inotropic agents, diets with at least 300 $mg \cdot day^{-1}$ are recommended for adult women, 350 $mg \cdot day^{-1}$ for adult men and 450 $mg \cdot day^{-1}$ during pregnancy [39]. These values should be higher, e.g. 450–500 $mg \cdot day^{-1}$, in adults suffering from CHF who do not have renal retention of Mg^{2+}, particularly when they are being treated pharmacologically. Patients suffering from CHF and with active anabolism should receive 7 mg $Mg^{2+} \cdot kg^{-1} \cdot day^{-1}$.

Optimization of sodium intake

It is desirable to determine the amount of dietary Na^+ that optimizes Na^+ balance and minimizes urinary Mg^{2+} and K^+ excretions in each patient suffering from CHF who is being chronically treated with a diuretic. For this purpose, a trial-and-error procedure should be followed whereby standardized diets with known Na^+, Mg^{2+} and K^+ contents are given for 5 days and the 24-hour urinary outputs of these cations are evaluated on the last day.

Selection of the diuretic substance and minimization of the diuretic dose

Cardiac oedema should be treated by attempts at reversing the primary cause (myocardial failure), by optimizing dietary salt intake and by therapy with common loop or distal tubular diuretics in the minimal doses compatible with necessary Na^+ and fluid mobilization. The amounts of Mg^{2+} and K^+ lost in the urine during treatment of oedema with diuretics are roughly proportional to the total amount of Na^+ which is mobilized (Tab. 4).

The velocity at which oedema should be suppressed in CHF patients is sometimes determined by a peremptory necessity to rid the lungs of water; high doses of diuretics are used in these circumstances, despite the risk of high Mg^{2+} and K^+ losses. Oral doses of diuretics higher than 40 $mg \cdot day^{-1}$ furosemide, 50 $mg \cdot day^{-1}$ hydrochlorothiazide, or doses of other diuretics with equivalent 24-hour natriuretic effect, may be required at the beginning of treatment if ascites, which impairs the absorption of diuretics, is present.

Patients suffering from CHF require chronic therapy with diuretics to allow excretion of Na^+ that would otherwise be retained [41, 43]. Loop diuretics should be preferred to distal tubular drugs when diuretics are given once daily, since loop diuretics have a milder 24-hour excretory action in subjects with steady-state mineral turnovers (Tab. 1–3) [31, 43, 47, 50] at this frequency of administration, and therefore are less likely to cause undue Mg^{2+}, K^+ and Na^+ losses than distal tubular diuretics. Hypokalaemia and hyponatraemia are definitely more frequently induced by distal tubular than by loop diuretics in CHF [41, 43]. Formulations that would appear

not to cause significant magnesiuresis (Tab. 3) and kaliuresis (Tab. 2), such as muzolimine 30 mg and torasemide 5 and 10 mg should be used once daily, in preference to furosemide 40 mg which provokes urinary Mg^{2+} losses (Tab. 3). When therapy with the suggested formulations does not attain the clinical objective sought, low-dose distal tubular diuretic formulations, e.g. hydrochlorothiazide 25 mg·day^{-1} or xipamide 10 mg·day^{-1}, should be used. Further needs for diuresis should be sequentially met by the utilization of standard doses of distal tubular diuretics, of combinations of standard doses of loop and distal tubular diuretics (e.g. 50 mg·day^{-1} hydrochlorothiazide and 40 mg·day^{-1} furosemide), and of combination therapy with a loop and a distal tubular diuretic at suprastandard doses.

Combination therapy with magnesiuretic and potassium-retaining diuretics

The coadministration of a K^+-retaining with a common diuretic potentiates the natriuretic action of the drug mainly acting at earlier nephronal portions. In addition, the coadministration of a K^+-retaining and a magnesiuretic diuretic diminishes the urinary losses of Mg^{2+} caused by the sole administration of the latter substance. This beneficial effect is more important when a K^+-retaining diuretic is coadministered with a loop diuretic than with a distal tubular substance; during the latter treatment the coincidental Ca^{2+}-retaining action of K^+-retaining and distal tubular diuretics results in hypercalcaemia, a decrease in the plasma concentration of PTH and a subsequent fall in Mg^{2+} reabsorption in the loop of Henle (Fig. 4) [42]. When a K^+-retaining substance is coadministered with a loop diuretic, the opposite effects of these drugs on urinary Ca^{2+} excretion minimize the possibility of changes in urinary Ca^{2+} output, and therefore of indirectly dependent rises in urinary Mg^{2+} output (Fig. 4).
When combination therapy is started at the onset of diuretic therapy it might have prophylactic value with respect to Mg^{2+} and K^+ depletions in some patients; nevertheless, the coadministration of a K^+-retaining diuretic can not be advocated as an advantageous routine therapeutic manoeuvre, since K^+-retaining diuretics have unwanted effects per se and are often inefficacious in preventing the somatic depletion of Mg^{2+} induced by distal tubular diuretics [30, 42].

Administration of magnesium salts

Magnesium salts should be administered prophylactically to those CHF patients treated with diuretics and/or digitalis at high doses or who are at risk of developing Mg^{2+} deficiency because of the coexistence of any unavoidable factor(s) which may predispose to the condition. Although the prophylactic value of this measure is still awaiting formal investigation, the innocuity and great potential usefulness of the manoeuvre definitely count in favour of its present enforcement. Doses of Mg^{2+} of 7.5 – 15 mmol·day^{-1}, divided between the two principal meals, should be prescribed to an adult male of 70 kg body mass. This dose should be doubled if evidence of Mg^{2+} depletion appears. These dosages should be lowered as appropriate in children. Any of the Mg^{2+} salts currently used for the oral prophylaxis and treatment of Mg^{2+} deficiency (aspartate HCl, chloride, citrate, gluconate, lactate, orotate) may be used.
The principal contraindications for oral Mg^{2+} administration are similar to those of intravenous diuretic therapy (vide infra).

Administration of potassium salts

In CHF with Mg^{2+} deficiency, plasma K^+ should be monitored during Mg^{2+} supplementation. Oral preparations of KCl should only be given when serum K^+ falls below 3.5 mmol·L^{-1}. Treatment should not be prolonged after the normalization of kalaemia, inasmuch as a high plasma K^+ concentration promotes aldosterone secretion and thus augments magnesiuresis, and because oral K^+ salts may provoke serious gastrointestinal side effects even when slow-release forms are used.

Pharmacological use of magnesium in the therapy of cardiac arrhythmias developing in treated congestive heart failure patients

Intravenous magnesium sulphate should be administered, as an immediate first therapeutic measure, when supraventricular or ventricular arrhythmias develop in CHF in general, and in particular when patients are receiving diuretics and/or inotropics, or when arrhythmias follow the superimposition of a myocardial infarction, not complicated by cardiogenic shock, on the CHF syndrome [5, 8, 11, 58]. A Mg sulphate solution can be given as a bolus of 2.5 g, which usually suppresses arrhythmias within 20 – 30 seconds, or as a slow (over a 1 – 3 minute period) intravenous injection of 3 or 4 g, or at a dose of 40 mg·min^{-1} in a saline infusion. A 20 % solution of Mg sulphate is usually employed for bolus and slow intravenous administrations. The infusion is

safe and can be continued indefinitely without any detectable rise in the serum Mg^{2+} level in most cases [5].

Intravenous Mg sulphate should not be administered to CHF patients who develop heart rhythm disturbances during myocardial infarction complicated by cardiogenic shock until the haemodynamic effects of Mg^{2+} in these circumstances are duly investigated, since intravenously administered Mg^{2+} has been found to cause arterial hypotension occasionally [13].

The contraindications for Mg^{2+} administration are myasthenia gravis, periodic hypermagnesaemic paralysis and an excessive accumulation of the cation, which sometimes occurs in patients with acute or chronic renal insufficiency with a glomerular filtration rate below 30 $ml \cdot min^{-1}$, hypothyroidism, viral hepatitis, Addison's disease, and treatment with lithium. Whether severe bradycardia and second or third degree atrioventricular block caused by digitalis constitute a therapeutic indication, option or contraindication for intravenous Mg^{2+} therapy in digitalis intoxication remains to be investigated. The presence of these conduction disturbances is a definite contraindication to intravenous Mg^{2+} administration when bradycardia and advanced atrioventricular block are not caused by digitalis. Phosphaturic nephritis is a transient and relative contraindication; the likelihood of phosphate precipitation by Mg^{2+} in the urinary tract should be weighed against the potential therapeutic benefit of intravenous Mg^{2+} therapy and the possible effectiveness and safety of alternative antiarrhythmic treatments.

Plasma Mg^{2+} levels should be monitored during prolonged infusions of Mg sulphate. Therapy should be withdrawn if plasma Mg^{2+} rises above 2 $mmol \cdot L^{-1}$. Since intravenous Mg^{2+} therapy may seldomly cause important arterial hypotension [13], blood pressure should also be monitored, and treatment should be discontinued or the infusion rate decreased if hypotension develops. Special care has to be exercised in patients with respiratory insufficiency, in whom Mg^{2+} therapy at high doses may impair ventilatory function further [13].

The intravenous administration of K^+ salts seems to suppress some serious ventricular arrhythmias provoked by diuretics and/or digitalis, but this effect is usually transient while the overall electrolyte derangement (low myocardial Mg^{2+} and high sarcoplasmic Na^+ and free cytosolic Ca^{2+} concentrations) remains uncorrected. It is however correct practice to coadminister KCl with intravenous Mg^{2+} when K^+ in plasma is below 3.5 $mmol \cdot L^{-1}$, 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.

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