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Ionic Disturbances in Hospital Practice: The Case for Magnesium

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Zusammenfassung

Die in der Krankenhauspraxis am meisten diagnostisch verkannten Abweichungen des Elektrolythaushalts sind die Hypo- und Hypermagnesiämie. Bei Hypokaliämie, Hyponatriämie, Hypophosphatämie und Hypokalziämie sollte der Kliniker sofort an eine möglicherweise vorhandene Hypomagnesiämie denken. Wird eine solche nicht erkannt und korrigiert, kann es zu einer hartnäckigen Kaliumdepletion kommen. Bei seinen mit Digitalispräparaten behandelten Patienten erwartet der Kliniker meist eher eine Hypokaliämie als eine Hypomagnesiämie.Dabei kann diese, öfter noch als eine Hypokaliämie, mit an der Toxizität von Digitalispräparaten beteiligt sein. Bei niereninsuffizienten Kranken wird gegebenenfalls nicht bemerkt, daß die Ursache hartnäckiger Hypotonie eine Hypermagnesiämie ist. Daher wird die routinemäßige Bestimmung der Magnesiämie im Krankenhaus die Diagnose und Behandlung von Hypo- und Hypermagnesiämie bedeutend verbessern.

Summary

Hypomagnesemia and hypermagnesemia represent the most underdiagnosed electrolyte abnormality in hospital practice. Hypokalemia hyponatremia, hypophosphatemia and hypocalcemia should alert the clinician to the possibility of associated hypomagnesemia. Refractory K repletion results from failure to recognize and correct coexisting hypomagnesemia. Clinicians are more aware of hypokalemia than hypomagnesemia in their patients receiving digitalis. Therefore, hypomagnesemia may be a more frequent contributor to digitalis toxicity than hypokalemia. Hypermagnesemia may go unrecognized as a cause of refractory hypotension in patients with renal insufficiency. Routine serum Mg determination in hospitals will significantly improve clinicians' ability to recognize and treat hypomagnesemia and hypermagnesemia.

Résumé

En pratique hospitalière, l'hypomagnésémie et l'hypermagnésémie représentent l'anomalie électrolytique dont le diagnotic est le moins souvent posé. Une hypokaliémie, une hyponatrémie, une hypophosphatémie et une hypocalcémie devraient alerter le clinicien sur l'éventualité d'une hypomagnésémie associée. La nonreconnaissance et l'absence de correction d'une hypomagnésémie associée peuvent entraîner une déplétion potassique rebelle. Les cliniciens sont plus conscients des problèmes d'hypokaliémie que des problèmes d'hypomagnésémie chez leurs patient sous traitement digitalique. En conséquence, l'hypomagnésémie peut contribuer plus fréquement à la toxicité des digitaliques peut que l'hypokaliémie. L'hypermagnésémie passer inaperçue en raison d'une hypotension rebelle chez les insuffisants rénaux. A l'hôpital, un dosage de routine de la magnésémie permettrait d'améliorer significativement le diagnostic et le traitement de l'hypomagnésémie et de l'hypermagnésémie.

Introduction

It is very likely that hypomagnesemia and hypermagnesemia represent the single most underdiagnosed serum electrolyte abnormality in hospital practice today. There are 2 clear reasons for this: 1) the pervasiveness of disorders in Mg metabolism in hospitalized patients and 2) the absence of routine serum Mg determination in hospitals.

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Etiology of Clinical Hypomagnesemia

The pervasiveness of hypomagnesemia and Mg depletion in clinical practice is illustrated by the 27 diverse clinical causes of hypomagnesemia [1]. These can be divided into 4 categories: 1) gastrointestinal, 2) renal, 3) endocrine and 4) miscellaneous. Another view might be that there are renal-related Mg losses and extrarenal causes of Mg losses. The extrarenal Mg losses are primarily gastrointestinal and secondarily endocrine in origin. Alternatively, Iseri has suggested the "10 D's for the causes of Mg deficiency": diarrhea, diuretics, diabetes, dietary deficiency, diverted to free fatty acids, drinking alcohol, drugs (cisplatinum, gentamicin, amphotericin, cyclosporin), decompensated heart, lungs, liver, delivery and pregnancy (toxemia, eclampsia) denuded skin, and burns [2].

Frequency of Hypomagnesemia and Other Electrolyte Abnormalities

Estimates of the incidence of hypomagnesemia reported by us and other groups indicate that overall the range is from 6.9 % in a Veterans Administration Hospital [3] to 11 % at a University Hospital [4]. Furthermore, the sickest hospitalized patients found in the Medical Intensive Care have the highest incidence of hypomagnesemia ranging up to 20 % [5]. We have recently exami-

ned the relative efficiency of identifying serum Mg abnormalities, both hypo- and hypermagnesemia, comparing physicians' orders versus performing Mg on a routine basis whenever serum electrolytes (Na, K, Cl, CO_2) were required in the care of patients [6]. A total of 1033 specimens were studied. Eighty one requests from physicians were received for serum Mg and 952 had Mg routinely performed without a physician's order. Routine serum Mg revealed a 9-fold increase in diagnosing hypomagnesemia (90 % vs 10 %) and better than an 8-fold increase in diagnosing hypermagnesemia (87 % vs 13 %) when contrasted to physicians' orders for serum Mg. In our opinion, this study clearly demonstrated the efficiency of routine serum Mg determination in identifying perturbations in Mg metabolism in hospitalized patients.

What are some electrolyte abnormalities associated with hypomagnesemia and hypermagnesemia in hospitalized patients? We have previously reported that hypomagnesemia was seen in 42 % of hypokalemic patients, 29 % of hypophosphatemic patients, 23 % of hyponatremic patients and 22 % of hypocalcemic patients [7]. Thus, in the absence of routine serum Mg determination, identification of hypokalemia, hypophosphatemia, hyponatremia and hypocalcemia should alert the clinician of the possibility of coexisting hypomagnesemia. Because of our interest in the interrelationship between Mg and K, we have recently reexamined the relationship between hypo- and hypermagnesemia and serum K [6]. Clinicians identified only 15–17 % of the hypomagnesemia in hypokalemic patients. Conversely, routine Mg determination demonstrated greater than an 8-fold increase in identifying hypomagnesemia in these hypokalemic patients compared to serum Mg determination done on physicians' orders (85 % vs 15 %). Our recent observations contrasting the efficacy of identifying hypomagnesemic patients by routine serum Mg determination demonstrated that clinicians are overlooking 85 % to 90 % of the hospitalized patients who are hypomagnesemic. Resolution of this problem is simple: perform serum Mg routinely whenever clinicians require electrolytes in the management of their patients.

Cardiac Arrhythmias and Hypomagnesemia

Depletion of K as well as Mg may result in cardiac arrhythmias. The EKG changes associated with hypokalemia and K depletion appear more characteristic than are the changes described for hypomagnesemia and Mg depletion. In hypokalemia S-T depression, T-wave voltage decrease, and increased U-wave voltage have been described. In contrast, widened QRS interval, peaking of the T-wave, prolongation of the P-R interval and S-T segment depression have been described [8]. Both hypokalemia and hypomagnesemia have been associated with ventricular tachycardia and ventricular fibrillation. Hypomagnesemia has, in addition, been related to torsade de pointes [9] and multifocal atrial tachycardia [10]. It is apparent then that hypomagnesemia and Mg depletion can lead to lethal ventricular arrhythmias and consequent sudden death. This is especially noteworthy in critically ill patients [2]. In these critically ill patients with refractory ventricular tachycardia and/or fibrillation, torsade de pointes, digitalis-toxic tachyarrhythmias, multifocal atrial tachycardia and hypomagnesemic atrial tachyarrhythmias, Iseri recommends the following regimen which has successfully controlled these previously refractory arrhythmias: 10–15 ml of 20 % $MgSO_4$ infused in 1 minute followed by 500 ml 2 % $MgSO_4$ in 5 hours. A second 500 ml of 2 % $MgSO_4$ over 10 hours may be necessary to control recurrence of arrhythmias. Onset of renal insufficiency, increase of serum Mg greater than 5 mEq/L, decrease in systolic blood pressure below 80 or pulse rate below 60 or loss of deep tendon reflexes constitute contraindications to the continued use of Mg [2].

Congestive Heart Failure, Digitalis Toxicity and K and Mg

Congestive heart failure is associated with a 5 year mortality which is approximately 50 %. Furthermore, the commonest cause of demise is sudden unexpected death (SUD) which accounts for nearly one half of these deaths [11]. The likelihood is great that that lethal ventricular arrhythmias account for the vast majority of these cases of sudden unexpected death in patients with congestive heart failure [12, 13]. What factor or factors play a role in arrhythmogenicity in these patients. Treatment of congestive heart failure with diuretics and digitalis may both be contributors to sudden death. Diuretics are both kaliuretic and magnesiuric [14]. Thus, hypokalemia and hypomagnesemia could contribute to digitalis toxicity. While clinicians are aware of the necessity of avoiding hypokalemia in patients receiving digitalis, the importance of avoiding hypomagnesemia may not be clinically appreciated. Our earlier study indicated that in digitalized patients clinicians were more adept at avoiding hypokalemia (9 %) than hypomagnesemia (19 %) [15]. Thus, in our opinion, hypomagnesemia may play a greater part in digitalis toxicity than does hypokalemia, perhaps by a factor of two. More recently we completed a second study examining the frequency of hypokalemia and hypomagnesemia in patients receiving digitalis. We contrasted the efficacy of routine determination versus the ability of the clinician to recognize the possibility of coexisting hypomagnesemia and to order serum Mg determination [16]. In this study we found that 100 % of the hypokalemic patients receiving digitalis were clinically recognized. In contrast, only 38 % of the hypomagnesemic patients were recognized by the clinician. Fully 62 % of hypomagnese-

mic digitalized patients were missed by clinicians. Thus, hypomagnesemia still exceeds hypokalemia as a greater potential contributor to digitalis toxicity. In our opinion both of our studies have demonstrated the effectiveness of routine serum Mg determination as well as K in identifying patients receiving digitalis who are at risk for electrolyte-induced toxic arrhythmias. It is important to recognize patients receiving digitalis who are hypomagnesemic because experimental [17] as well as clinical observation [18] demonstrated the effectiveness of Mg in controlling digitalis-induced arrhythmias. In a variety of species (dogs and cats) bolus injection of $MgSO_4$ or $MgCl_2$ induced an 81 % to 100 % response to digitalis-induced arrhythmias [17]. In man, the administration of Mg ameliorated 56 % of digitalis-induced supraventricular arrhythmias whereas Mg was effective in 92 % of patients with ventricular arrhythmias associated with digitalis toxicity [17]. In summary, routine serum Mg determination in patients with congestive heart failure may materially assist in identifying patients requiring administration of Mg. Early identification and treatment with Mg may decrease the number of sudden unexpected deaths by ameliorating the frequency of lethal ventricular arrhythmias in those patients who frequently receive both digitalis and diuretics. Routine serum Mg determination will identify digitalis toxic hypomagnesemic patients who are presently unidentified.

Hypertension and Hypomagnesemia

The effect of Mg in lowering blood pressure is well known. Hypomagnesemic hypertensive patients required more antihypertensive medications to maintain blood pressure control when compared to normomagnesemic hypertensives [19]. In contrast to the studies in digoxin-treated patients where the incidence of hypomagnesemia exceeded hypokalemia by a wide margin [15, 16] in 1000 ambulatory hypertensive patients we found that hypokalemia (17 %) exceeded hypomagnesemia (4.5 %) [19]. *Dyckner* has reported that Mg supplementation enhanced the hypotensive effect of diuretic therapy [20]. Karppanen has reported on the beneficial effect of a new oral salt containing lesser amounts of Na by partial substitution with Mg and K (Na-K-Mg Salt) on blood pressure [21]. This K and Mg enriched salt has been further refined to include lysine monohydrochloride (Pansalt). What mechanism or mechanisms are responsible for the hypotensive effect of Mg? Rude has proposed that prostacyclin release through changes in Ca^{++} flux may be the vasodilatory mechanism of Mg-induced decrease in blood pressure [22]. This group also proposed that Mg may be an antagonist through the mediation of Ca^{++} of the pressor and steroidogenic effects of angiotensin II. Infusion of 200 mg Mg per hour resulted in statistically significant decreases in systolic and diastolic pressures in human subjects. On the other hand, infusion of Mg in the presence of a cyclooxyglenase inhibitor (Indomethacin or Ibuprofen) or a calcium channel blocker (Nifedipine) did not affect either blood pressure or prostacyclin secretion (no increase in urinary 6-keto-PGF_1). Under stringent, controlled circumstances Rude's group induced dietary Mg deficiency in human subjects for a period of 3 weeks. Note that hypomagnesemia ensued, decreasing from 1.9 ± 0.2 to 1.3 ± 0.2 mg/dl. At the same time the 24 hour urinary Mg retention test demonstrated a statistically significant increase, rising from 12 % to 65 % retention, indicating the presence of Mg deficiency [23]. Note that these data, as in numerous other experimental and clinical studies, indicate that hypomagnesemia resulting from depletion of Mg is consistent with and indicative of Mg deficiency. Therefore, in our opinion, it is of clinical importance to identify all hospitalized patients who are hypomagnesemic and Mg deficient and who require Mg repletion. The effect of Mg infusion and Mg depletion on the pressor responses to Angiotensin II (AII) demonstrated that Mg infusion diminished the pressor effects of AII whereas a deficiency of Mg resulted in enhanced pressor response to AII infusion. These observations are consistent with the view that the vasodepressor effects of Mg may be via enhanced prostacyclin secretion and that the vasopressor effects of Mg deficiency may result from enhanced response to Angiotensin II with both mechanisms mediated through changes in Ca^{++} flux [22].

Refractory K Repletion and Hypomagnesemia

Magnesium and K, the principal intracellular cations, are closely articulated at the cell level. Experimental and clinical observations indicate that Mg deficiency is associated with a loss of cell K which ensues despite provision of K [24, 25]. Furthermore, both kaliuresis and phosphaturia accompany Mg depletion [24]. With K depletion in rats, superimposition of Mg deficiency results in a greater degree of cell K depletion compared to K depletion alone [26]. Mg appears important not only in maintenance of cell K but also plays an important role in the repletion and restoration of cell K. In rats depleted of both K and Mg, simultaneous repletion of both K and Mg resulted in a statistically significant increase in muscle K content compared to repletion with K alone [27]. This observation indicated the pivotal role of Mg in restoring cell K following a period of K depletion and Mg depletion. Furthermore, this study also demonstrated the importance of recognizing and repleting any coexisting Mg depletion so as to optimize cell K repletion. Thus our demonstrating the importance of recognizing and treating coexisting Mg depletion in optimizing cellular K repletion constitutes the experimental basis for the clinical diagnosis of refractory K repletion due to Mg

depletion [28]. We have suggested the possibility that there are 2 types of refractory K repletion: Type A in which hypokalemia is not corrected with administration of K until the coexisting hypomagnesemia is recognized and treated. The second type of refractory K repletion (Type B) related primarily to intracellular K deficits which do not correct with K alone but is when Mg as well as K is provided [29]. Our most recent experience with refractory K repletion due to coexisting Mg depletion and hypomagnesemia occurred in 2 patients receiving Cisplatin therapy, one for seminoma and the second for squamous cell carcinoma of the tonsil [30]. Cisplatin causes renal K and Mg wasting, resulting in concurrent hypokalemia and hypomagnesemia [31]. Because serum Mg is not a routinely measured analyte it is important for the clinician to recognize the possibility of coexisting hypomagnesemia in Cisplatin-treated patients. In these 2 cases, hypokalemia was refractory to treatment with K until the coexisting hypomagnesemia was recognized and treated. These 2 cases represented Type A refractory K repletion manifested by refractory hypokalemia. Our group has surveyed tha literature for similar cases of refractory K repletion due to concurrent Mg deficiency. A total of 73 cases were compiled [29]. Diuretic therapy, especially with loop blockers, represented the largest single cause of refractory K repletion. Note that diuretics were primarily utilized to treat patients in congestive heart failure, representing 63 % of this series. The most direct clinical approach to detecting and treating coexisting hypomagnesemia to avoid the problem of refractory K repletion is to routinely measure serum Mg [3, 32].

What mechanism(s) underlie the problems of refractory K repletion due to concurrent Mg depletion? Current observations suggest that deficiency of Mg may result in alteration in cell membrane characteristics, impairment of Mg activated cellular cation pump function and/or diminished Na-K pump density [33]. *Schilling* et al. described accelerated cell K loss due to altered cell membrane characteristics resulting from Mg depletion in *Ehrlich* ascites tumor cells [34]. In this study, cell K loss and intracellular Na accumulation resulted when the Na-K pumps could not keep pace with the accelerated intracellular K loss. Recently, *Dorup*'s group observed diminution in the Na-K pump density in skeletal muscle associated with Mg depletion [35]. This group has "closed the loop" by reporting that Mg repletion normalized the Na-K pump density and corrected the muscle K depletion [36].

Hypermagnesemia

In 2 separate studies our data indicate that when serum Mg is performed routinely in hospitalized patients, hypermagnesemia is detected with the frequency of 5.5 % [3] to 7.8 % [6]. Furthermore, our most recent study demonstrates that clinicians are detecting only 12 % to 13 % of the cases of hypermagnesemia [6]. In contrast routine serum Mg determination detects about 87 % of the hypermagnesemic cases. Thus, as in the case for hypomagnesemia, routine serum Mg determination far exceeds the ability of clinicians to detect hypermagnesemia on clinical grounds. By far that commonest clinical setting for hypermagnesemia is acute renal failure or chronic renal failure with exogenous Mg intake or Mg administration for treatment of toxemia [37]. Progression of clinical signs and symptoms range from hypotension to nausea, vomiting and cutaneous flushing to mental changes, decreased reflexes, decreased respiration to coma and finally cardiac arrest. Hypermagnesemia ranges from 2.5 to 4.5 mEq/L which is associated with hypotension to decreased respirations at 10–14 mEq/L. Refractory hypotension in a patient with renal insufficiency should alert the clinician to the possibility of significant hypermagnesemia [38, 39, 40]. As in the case of hypomagnesemia, routine serum Mg will significantly assist the clinician in detecting patients with hypermagnesemia.

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