Circulating total and ionized magnesium after ethanol ingestion

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Hypomagnesemia is associated with alcoholism (Lim P, Jacob E. Metabolism 1972;21:1045–51). Here we assess two measurements of blood magnesium in emergency care patients with confirmed ethanol ingestion. Serum total and ionized magnesium (tMg, iMg) were measured in 88 patients with ethanol concentrations of 6–128 mmol/L and in sera of 97 hospitalized patients (control group). iMg was measured by an ion-selective electrode method; tMg was measured spectrophotometrically. iMg was significantly lower for the ethanol-containing specimens (0.35 ± 0.12 mmol/L, mean ± SD) than for the control group (0.46 ± 0.15 mmol/L), with P < 0.0001. The tMg for the test group (0.87 ± 0.20 mmol/L) was not significantly different from the controls (0.88 ± 0.33 mmol/L), with P = 0.3987. tMg was not well-correlated with iMg in the ethanol-positive specimens. Most ethanol-positive patients had abnormally low serum iMg (87 of 88 had iMg <0.53 mmol/L).

INDEXING TERMS: alcoholism • hypomagnesemia • ion-selective electrodes • abused drugs

Magnesium is a cofactor for >300 enzyme systems and the second most abundant intracellular cation in the human body [1]. Mg deficiency is associated with central nervous system, cardiac, and metabolic abnormalities, e.g., hypertension, delirium, tremor, and hypocalcemia. Hypomagnesemia was described in chronic alcoholics in the late 1960s [2–4]. Studies on the etiology of hypomagnesemia in alcoholism ascribed it to reduced intake, decreased absorption, or increased urinary excretion [3, 5]. Administration of Mg is recommended as a replacement therapy for treatment of alcohol withdrawal syndrome if symptoms of hypomagnesemia are present or if refractory hypocalcemia is diagnosed in a chronic alcoholic [6, 7].

The introduction of ionized Mg (iMg) measurement by ion-selective electrode (ISE) has brought a resurgence of interest in Mg status and hypomagnesemia [5] because the free circulating Mg may be the physiologically reactive portion in dynamic states. The circulating iMg concentrations in alcoholics have not been studied, nor has the effect of ethanol consumption on iMg been described. The association of blood iMg with clinical status in alcoholics is unknown, as is the relation of circulating iMg to total Mg (tMg). When ISE measurements were initially introduced, a report based on analysis of normal individuals suggested that the relation of tMg to iMg was stable enough to predict tMg from iMg measurement [8], but the conclusions were limited to that group. More recent studies have shown that iMg may fluctuate significantly with little change in tMg concentration in selected patient populations, including those with migraine, head trauma, non-insulin-dependent diabetes mellitus, and asthma [9].

Given this background, when inebriated patients present to a hospital emergency service with acute hypomagnesemia symptoms today, a “stat” tMg measurement may be ordered. However, iMg measurement by ISE is technically a more practical and rapid analysis for emergency laboratory services because the assay can be performed on whole blood. As a first step toward examining the usefulness of blood iMg in management of alcoholics, we decided to study the iMg and tMg concentrations in ethanol-positive patients. The goals of this work were to: (a) determine whether the iMg concentrations would be correlated to the tMg concentrations in this population, (b) compare iMg concentrations in ambulatory ethanol-positive patients with the reported reference ranges, and (c) determine whether the incidence of hypoionized magnesium in ambulatory ethanol-positive patients seen in a trauma hospital emergency department differs from that expected in a cohort of hospitalized patients.

Materials and Methods

CLINICAL SPECIMENS
Two groups of specimens were examined. The first consisted of 88 sera with positive ethanol content drawn from patients presenting at the emergency department in a large urban trauma hospital. In this institution, alcoholic patients are rehydrated only as indicated from clinical and laboratory evaluation. As

1 Nonstandard abbreviations: iMg, ionized Mg (Mg2+); ISE, ion-selective electrode; and tMg, total Mg.

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these were the first specimens taken from the patients, they reflect the condition of the blood before extensive hospital-based intervention. The ethanol in these specimens ranged from 6 to 129 mmol/L.

The second group of specimens consisted of 97 sera from hospitalized patients. They were assumed to be an alcohol-free control group for two reasons: First, ethanol is inaccessible to these patients. Second, these patients were undergoing a variety of physiological stresses, which are similar to those of acute care in the emergency department. The Human Subjects Committee of the University of Washington, which subscribes to the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 1983, approved the use of patient specimens in this study.

All specimens were collected in the same brand of anticoagulant-free blood collection tube (Becton Dickinson, Rutherford, NJ). They were either analyzed on the day of receipt in the laboratory or stored frozen in sealed tubes until they could be analyzed the next day.

**ANALYTICAL METHODS**

Ethanol was measured with a Shimadzu (Kyoto, Japan) GC-14A gas chromatograph [10, 11]. iMg and pH were measured with electrodes with a Nova 8 analyzer (Nova Biomedical, Waltham, MA) [12]. tMg was measured by a colormetric calmagite binding technique with a Paramax automated analyzer (Baxter Diagnostics, Santa Ana, CA) [13].

**STATISTICAL ANALYSIS**

The StatView 4.5 statistics program (Abacus Concepts, Berkeley, CA) was used for all data analysis. Mean values and standard deviations were calculated and tested for difference by a two-tailed Student's t-test. A P ≤0.05 was considered significant.

**Results**

**iMg and tMg (in Clinical Sample Groups)**

Table 2 shows the statistical summary of iMg and tMg analysis on the ethanol-positive and control specimen groups. In addition, the percent of tMg attributable to measured iMg was calculated and data for each specimen set are given. Fig. 1 shows the percentile distribution of the iMg and tMg in both groups. The mean iMg for the test group (0.35 ± 0.12 mmol/mL, mean ± SD) was lower than for the controls (0.46 ± 0.15 mmol/mL) and the difference was significant by the Student's t-test (P <0.0001). By contrast, there was no significant difference between the tMg means measured (0.87 ± 0.20 mmol/mL for ethanol-positive specimens vs 0.88 ± 0.33 mmol/mL for ethanol-free specimens, P = 0.5987). The percent of the tMg attributed to iMg (iMg/tMg) in ethanol-positive specimens varied by a range of 37%, whereas the range of variation in the control group was 38%. Examination of Fig. 1 shows that the percentile distributions of iMg in the two sets of samples have very similar profiles. The highest iMg in the ethanol-positive specimens, 0.54 mmol/L, is the only one close to the reported normal range for this analytic, making 99% of these samples in the hypomagnesemic range by the iMg criteria (0.53 mmol/L) [12]. The iMg values of the hospitalized patients include both normal and abnormally increased results, with 79% below the reported lower limit of normal for healthy individuals [12]. The percentile distributions of tMg for both groups were of a similar profile, and the values overlay each other in the plot. Considering tMg, 6.8% of the ethanol-containing specimens had results below the lower limit of normal (0.75 mmol/L), whereas 12% of the control specimens had results <0.75 mmol/L.

The amount of iMg as a percent of tMg showed a mean of 40.5% (range 22.0–58.8%) for ethanol-positive specimens and 54.1% (range 40.0–77.8%) for the control group. Both values are lower than the range reported in the literature (61.1–84.5% with a mean of 71%) [12].

The iCa/iMg ratios were calculated for both groups. The iCa/iMg for ethanol-positive specimens was 3.140 ± 0.594 mmol/L (mean ± SD), with a range of 2.102–4.773 mmol/L. For the control specimens, the comparable data were 2.227 ± 0.333 mmol/L and 1.067–2.861 mmol/L.

**Table 1. Effect of added ethanol on iMg (mmol/L) in serum measured by ISE.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>0</th>
<th>50</th>
<th>100</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.325</td>
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<td>0.285</td>
</tr>
<tr>
<td>2</td>
<td>0.505</td>
<td>0.510</td>
<td>0.490</td>
</tr>
<tr>
<td>3</td>
<td>0.490</td>
<td>0.470</td>
<td>0.490</td>
</tr>
</tbody>
</table>

**Table 2. Statistical description of iMg, tMg, and %iMg in ethanol-positive specimens and ethanol-negative specimens.**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Ethanol-positive specimens*</th>
<th>Ethanol-negative specimens*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>iMg (mmol/L)</td>
<td>tMg (mmol/L)</td>
</tr>
<tr>
<td>n</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Mean</td>
<td>0.349</td>
<td>0.865</td>
</tr>
<tr>
<td>SD</td>
<td>0.007</td>
<td>0.011</td>
</tr>
<tr>
<td>Minimum</td>
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<td>0.50</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.54</td>
<td>1.05</td>
</tr>
<tr>
<td>Variance</td>
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<td>0.011</td>
</tr>
<tr>
<td>Median</td>
<td>0.350</td>
<td>0.850</td>
</tr>
<tr>
<td>Range</td>
<td>0.330</td>
<td>0.550</td>
</tr>
</tbody>
</table>

*From patients presenting in hospital emergency room.

*From patients (control group).
CORRELATIONS

Figure 2 shows the correlation of iMg with tMg for the test (A) and control (B) groups. The regression equations were iMg (mmol/L) = 0.244 + 0.12 tMg (mmol/L) for the ethanol-positive specimens, and iMg = 0.176 + 0.329 tMg for the controls. The coefficients of determination were R² = 0.035 (r = 0.186; P = 0.083) and R² = 0.555 (r = 0.745; P < 0.001), respectively, so that only 3.5% of the variation in iMg was attributable to shifts in tMg in ethanol-containing specimens, down from 55.5% in controls. Fig. 3A presents the scatter plots of serum iMg and ethanol in the test group of specimens. The relation is inverse, with a regression equation of iMg = 0.386 – 0.001 ethanol. The coefficient of determination was R² = 0.075 (r = -0.274; P = 0.0095). Fig. 3B shows the simple regression plot of tMg with ethanol concentration in the test group. The regression equation for serum tMg and ethanol was tMg = 0.878 – (2.407 × 10⁻⁴) ethanol, and the coefficient of determination was R² = 0.004 (r = -0.0632; P = 0.5773). These results show that ethanol is more likely to influence serum iMg than tMg, that the influence is negative with increasing ethanol concentrations, but that the influence is very slight, accounting for only 7.5% of the change in the iMg.

Because iMg concentration in serum is known to be influenced by pH, the correlation of these variables in both specimen groups was examined. The simple regression equations for iMg (y) vs pH (x) for ethanol-positive specimens and for controls were: y = 1.881 – 0.199x and y = 2.027 – 0.201x, respectively, confirming the inverse relation of these variables in both groups. The correlation coefficients for the same data were -0.273 (P = 0.0098) and -0.546 (P = 0.0001), respectively, with coefficients of determination (R²) of 0.075 and 0.298, respectively. Thus, we estimate that only 7.5% of the variation of iMg seen in the ethanol-positive specimens was associated with pH, an almost fourfold decrease from that seen in the controls.

Discussion

This is the first description of circulating iMg in a large group of ethanol-positive patients. Their specimens are unusual in that the fraction of the tMg that is iMg is decreased. The factor or
Of possible physiological explanations, three may be considered: (a) selective excretion of iMg (relative to tMg) by the kidney after ethanol consumption; (b) iMg redistribution from blood into tissue; or (c) redistribution of circulating free Mg to a second circulating pool, e.g., by being sequestered into a protein-bound or complexed circulating form. The latter explanation—circular complex formation and binding in circulation—is supported by the lower fraction of tMg represented by iMg in the ethanol-positive specimens. Given the limited focus of this study, nothing more can be inferred from it. However, Flink has reported that free fatty acids cause the reduced tMg sometimes seen after alcohol ingestion [3]. We infer that iMg would be more sensitive to circulating fatty acids than tMg, as the latter would change only after the insoluble Mg-fatty acid complexes were removed from circulation. Rayssiguier administered epinephrine to sheep and observed that the circulating fatty acid concentration increased and the tMg decreased as a result [15]. This mechanism of increased lipolysis is relevant to the depletion of tMg associated with alcohol withdrawal [3].

The frequency and magnitude of depressed serum iMg concentrations from the ethanol-positive patients were greater than those in the control group, the selection of which was intended to account for stresses of the clinical setting or medical emergencies and which in its turn has depressed iMg relative to healthy controls.

The population from which the test specimens were taken was a mixture of both chronic alcoholics and casual drinkers who had in common acute symptoms of ethanol ingestion upon their arrival in a trauma hospital emergency department. The results therefore should not be directly extrapolated to alcoholics per se. That extension requires further investigation. Both the history of alcohol abuse, with its physiological sequelae, and the nutritional status of the emergency room patients in this study are probably mixed, i.e., not completely typical of alcoholics as a group. Moreover, the incidence of hypomagnesemia by serum tMg measurement reported here is far less than is described for documented alcoholics. For example, Heaton et al. [16] reported a 30% incidence of hypomagnesemia on the basis of tMg measurements. We speculate that serum iMg values in a true population of alcoholics will be more depressed than those described here.

On the other hand, the mean serum iMg reported here for the control group of hospitalized patients is identical to that described by Hristova et al., who used the same instrument, for 20 hospitalized patients [17]. The decrease in iMg seen in hospitalized patients may be a combination of nutritional and stress factors. Because serum iMg concentrations are significantly lower in a hospitalized patient population than in a healthy ambulatory group, the former was considered a more appropriate control group for this study.

Flink has suggested that the hypomagnesemia of alcoholism may be a cause of the neurological damage seen in chronic alcoholics [3]. The iMg depletion resulting from ethanol ingestion suggested by this study would be consistent with this hypothesis. Further study is needed to determine how iMg concentrations relate to the clinical signs, symptoms, and adverse effects of alcoholism. Finally, Elin [1] has pointed out the factors influencing this redistribution of free cation in circulation diminished the expected iMg dependence on, or at least association with, the specimen pH and tMg. We were not able to explain the findings as in vitro artifacts when we examined the two most likely nonphysiological causes. First, the ISE test system was not significantly influenced by ethanol. Second, the pHs of both test and control specimens were comparable, so alcalinization of test specimens during storage was eliminated as a cause of the relatively lower iMg values. We infer that, given the observation that all patients had depressed iMg values, this was an acute direct response to ethanol ingestion or its metabolites, whether direct or indirect. Our results are consistent with the report of Altura et al. [9], who observed decreased blood iMg in those with migraines, renal transplant patients, and others who were nonetheless normomagnesemic by the tMg criteria. Such reports have led to the suggestion that the iMg/tMg ratio may be clinically useful [9].

The difference in iCa/iMg ratio shown for our two groups is additional support for a pathological origin for our observations. Altura et al. [9] have used this ratio to describe several groups of patients with abnormal iMg results. In the case of head injuries, they indicated that the severity of the injury was correlated to the higher ratios.
difficulty of determining the most appropriate marker for overall body Mg status. This work demonstrates that iMg is probably an unsuitable marker for body Mg status in alcoholics. However, it also suggests that iMg might be a more sensitive test than tMg to monitor changes in circulating Mg status for patients after ethanol ingestion.

We draw three conclusions from this study. First, decreased circulating iMg is common, if not universal, in an acute-care population presenting with ethanol ingestion. Second, the presence of abnormally low iMg per se in this patient group does not signal the presence of any of the other reported causes of altered iMg/tMg ratios, e.g., malnutrition, migraine, diabetes, etc. As neither the mechanism nor the clinical significance of the altered iMg/tMg ratio in the alcohol-positive patients is understood, further research is needed. Finally, this study raises the potential that iMg may prove to be an important tool—more sensitive than tMg—in assessing appropriate management of patients withdrawing from alcohol and who may be at risk for the adverse effects associated with hypomagnesemia.

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References