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IFCC Guideline for sampling, measuring and reporting ionized magnesium in plasma[1),2)]

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[3)]

IFCC Scientific Division Committee on Point of Care Testing[4)]

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Abstract

Analyzers with ion-selective electrodes (ISEs) for ionized magnesium (iMg) should yield comparable and unbiased results for iMg. This IFCC guideline on sampling, measuring and reporting iMg in plasma provides a prerequisite to achieve this goal [in this document, ''plasma'' refers to circulating plasma and the forms in which it is sampled, namely the plasma phase of anticoagulated whole blood (or ''blood''), plasma separated from blood cells, or serum].

The guideline recommends measuring and reporting ionized magnesium as a substance concentration relative to the substance concentration of magnesium in primary aqueous calibrants with magnesium, sodium, and calcium chloride of physiological ionic strength. The recommended name is ''the concentration of ionized magnesium in plasma''. Based on this guideline, results will be approximately 3% higher than the true substance concentration and 4% lower than the true molality in plasma.

Calcium ions interfere with all current magnesium ion-selective electrodes (Mg-ISEs), and thus it is necessary to determine both ions simultaneously in each sample and correct the result for Ca^{2+} interference. Binding of Mg in plasma is pH-dependent. Therefore, pH should be measured simultaneously with iMg to allow adjustment of the result to pH 7.4.

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[4)] The current membership of the Committee on Point of Care Testing is as follows: Chairman: Anthony O. Okorodudu (USA); Members: M.C. Ben Rayana (TN); N. Fogh-Andersen (DK); Ch. Ritter (AT); Andrew St John (AU).

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The concentration of iMg in plasma may be physiologically and clinically more relevant than the concentration of total magnesium. Furthermore, blood-gas analyzers or instruments for point-of-care testing are able to measure plasma iMg using whole blood (with intact blood cells) as the sample, minimizing turnaround time compared to serum and plasma, which require removal of blood cells.
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Keywords: erythrocyte effect; heparin; influence factors; interference; ionized calcium; ionized magnesium; ion-selective electrode; lipophilic anions; liquid junction potential; pH; protein; sampling; silicone; sodium.

Contents

1. Introduction

1.1 Background

Magnesium fractions in plasma are in equilibrium and comprise magnesium ions, protein-bound magnesium and complex-bound magnesium. Ionized magnesium (iMg) refers to free magnesium ions (Mg^{2+}) that exist in hydrated form (1). Bound magnesium comprises several species that are distinguished in clinical chemistry on the basis of their molecular size as non-ultrafiltrable protein-bound magnesium (mainly to albumin) and ultrafiltrable complex-bound magnesium (mainly to bicarbonate, carbonate, lactate, phosphate and citrate) (2).

The equilibrium between free and bound magnesium is influenced by temperature, ionic strength, hydrogen ions (pH) and other ions competing with magnesium for binding sites. Under normal physiological conditions the fractions are: ionized magnesium, 59%–72%; complexed magnesium, 5–11%; and protein-bound magnesium, 23%–31% (3–6).

1.2 Purpose

Recent progress in sensor technology and instrumentation has made possible the measurement of iMg by magnesium ion-selective electrode (Mg-ISE) (7).

The Mg-ISE changes its electrical potential as a function of the chemical potential of the Mg^{2+} in solution. Since no perfectly specific Mg-ISE is available, this function is given by the Nikolsky-Eisenman equation, which is a modified Nernst equation (8).

Living cells respond to the activity of free hydrated magnesium ions in plasma and interstitial fluid. Total magnesium includes iMg (free magnesium) and magnesium bound to protein and anionic ligands, and its substance concentration depends on the water concentration of the sample. On the contrary, iMg is independent of the water concentration of the sample. It reflects the biological activity of Mg^{2+} ions and may be often more relevant in patient care than total magnesium concentrations, especially when a disturbed protein concentration can be expected, as often observed in critically ill patients (9–12). Furthermore, iMg can be measured in whole blood, minimizing turnaround time compared to the measurement of total magnesium in plasma, which requires previous removal of blood cells.

All analyzers with Mg-ISEs should yield comparable and unbiased results for iMg, independent of the instrumentation, and these results must be identical for serum, plasma and blood. A prerequisite to achieve this goal is to reach a consensus on sampling, measuring and reporting.

2. Sampling and storage

2.1 Sampling

The substance concentration of iMg can be measured in plasma or whole blood. If venous blood is used, sampling should preferably take place without a tourniquet and with the patient sitting at rest to assure a state of equilibrium. Any muscular action such as pumping should be avoided. Tubes coated with silicone or containing a silicone separator should not be used as collection devices to avoid the silicone effect (13, 14) (see section 2.1.1).

Application of electrolyte-balanced heparin as an anticoagulant is preferred. Since heparin binds magnesium, the minimum amount of heparin necessary should be used. When liquid heparin is used, it dilutes

the plasma. Plasma is also diluted when using dried heparin, because water leaves the erythrocytes to restore osmotic equilibrium between erythrocytes and plasma. In both instances the effect on iMg in plasma is negligible provided the minimum volume or amount of magnesium-balanced heparin necessary is used; 15 IU/mL Li, K or Na heparin and up to 50 IU/mL Mg-balanced heparin do not exert an error exceeding the imprecision of the measurement (error less than 1.5%). Careful mixing is necessary immediately after sampling to ensure proper anticoagulation. Centrifugation should be performed using a relative centrifugal force of $2000 \times g$ for 10 min. After centrifugation the supernatant should be separated as soon as possible (13, 15, 16).

The substance concentration of iMg in plasma depends on pH, mainly because the binding of magnesium to albumin increases with pH. pH should be maintained after sampling by preventing loss of CO_2 and glycolysis. Details of how this may be achieved may be found in two IFCC recommendations (17, 18).

2.1.1 Silicone effect The silicone effect is a non-specific surfactant effect that in principle may lead to substantial changes in ion-extraction conditions at the Mg-ISE and falsely elevated results. Several authors have observed this effect when silicone-coated vials or silicone-containing separator gels are used in sampling. The effect has not been observed for heparinized vials without silicone coating (13, 14).

2.2 Storage

Plasma samples can be stored for up to 1 month at +4°C. This period may be extended up to 3 months at –80°C (19). Blood is not suitable for storage, as hemolysis increases iMg. Minor hemolysis is acceptable.

3. Measurement

The potentiometric measurement of the substance concentration of iMg by Mg-ISE is the method of choice in clinical chemistry. The measurement system basically comprises an Mg-ISE and a reference electrode. On the sample side these two electrodes are bridged by calibrator, plasma or blood. Two electrical leads connect the electrodes to a voltmeter, which measures the potential difference (E). E is formally equal to the electrical potential difference between the Mg-ISE and the reference electrode and a salt bridge. After the system has been calibrated, $E_{Mg\text{-}ISE}$ of the sample is compared to the values for the calibrators. Using a chemometric procedure, e.g., an algorithm related to the Eisenman-Nikolsky equation, the substance concentration of iMg in the sample is then calculated.

3.1 Magnesium ISE

The main part responsible for signal formation of the Mg-ISE is its membrane (8, 20). In current instruments it is a plasticized PVC membrane in which the active compounds, i.e., the ionophore and additives, are dispersed. All currently available Mg-ISEs are not sufficiently selective and consequently several ions, substances and drugs may interfere with measurement of the substance concentration of iMg.

3.2 Reference electrode

A half-cell of constant potential is required, but is not fully achievable. The practical half-cell comprises an inner element, e.g., a silver-silver chloride electrode (Ag|AgCl), and a chamber containing filling solution, e.g., a concentrated solution of potassium chloride (>2 mol/L) contacting the solutions measured. The contact can be in the form of a constrained liquid junction, e.g., cellophane foil or porous ceramic plug, or an open liquid junction. Regardless of the design of this contact, a liquid junction potential will contribute to the electrical potential difference measured and may lead to significant analytical error (21, 22).

3.2.1 Liquid junction potential The liquid junction potential (E_j) contributes to E, along with the potential of the Mg-ISE ($E_{Mg\text{-}ISE}$) and the reference electrode (E_{ref}). In the measurement of divalent ions such as Mg^{2+}, the influence of the liquid junction potential has to be carefully considered. The values of E_j and ΔE_j (the residual liquid junction potential: plasma vs. calibrant) can be calculated using numerical methods (22) or estimated according to the Henderson equation (23).

3.2.2 Design of the liquid junction An open liquid junction is recommended to provide uncontaminated and undiluted bridge solution for each measurement.

A restricted liquid junction with a porous plug, or membrane, separating the reference electrode filling solution and the sample is permissible provided that similar results are obtained as those with a hypertonic open liquid junction. This limitation is due to the diffusion of rinse solution or sample into the porous plug, which dilutes the bridge solution, or washout effects and possible uncontrolled concentration change of the bridge. If the bridge solution is diluted, ΔE_j may be much larger than with a properly working open liquid junction, which increases the bias.

3.2.3 Erythrocyte effect on the liquid junction potential Erythrocytes lower E_j by approximately 1 mV (depending on hematocrit), with corresponding bias of at least +8% for iMg as measured with a bridge made of saturated KCl. Water extracted from erythrocytes near the hypertonic salt bridge solution dilutes the plasma and restores the osmotic equilibrium across the erythrocyte membrane (24). Diffusion potentials between plasma, diluted plasma and bridge solution are the major contributors to E_j observed with blood. The erythrocyte effect on E_j can be eliminated using a slowly flowing liquid junction, which eliminates the gradients in water concentration.

Table 1 Composition of calibration solutions to cover the clinically relevant range.

Calibrator	cMgCl$_2$, mmol/L	cCaCl$_2$, mmol/L	cNaCl, mmol/L
No. 1 (Low)	0.30±0.005	2.00±0.005	152.55±0.05
No. 2 (Medium)	0.60±0.005	1.25±0.005	153.90±0.05
No. 3 (High)	0.90±0.005	1.25±0.005	153.00±0.05

3.3 Calibration

Three primary calibrators of different concentrations of magnesium chloride (cMgCl$_2$), calcium chloride (cCaCl$_2$) and sodium chloride (cNaCl) should be used (Table 1) to calculate the standard potential, slope and selectivity coefficient for calcium of the Mg-ISE according to the Nikolsky-Eisenman equation (8). It is assumed that other ions, e.g., sodium, do not interfere.

The concentration of NaCl should be adjusted to yield ionic strength I_m=0.16 mol/kg. The calibration and measurement should be carried out at 37°C. The pH should be adjusted with 1 mmol/L HEPES buffer (pK_a=7.31 at 37°C) to yield pH 7.40 at 37°C.

Calibration during routine operation of the Mg-ISE can be performed with traceable calibrators, which may have additional functions, e.g., allowing calibration of other sensors (1).

3.4 Analytical influence factors

3.4.1 Interferences by calcium ions Calcium ions (Ca^{2+}) interfere with all current Mg-ISEs, and thus it is necessary to determine both ions simultaneously in each sample and correct the result for Ca^{2+} interference according to the known selectivity of magnesium over calcium. This is of special importance because all current Mg-ISEs are known to change their selectivity properties with time (25). Detailed calibrator compositions and the correction used in a particular instrument should be disclosed by the manufacturer. A minimum requirement is to have access to uncorrected values during calibration.

3.4.2 Interference and influence by sodium ions Analytical interference by sodium ions (Na^+) in Mg-ISE measurements is of the same type as that of calcium ions, although to a lesser extent, with a resulting error of not more than a few percent. The effect is augmented by sodium and chloride ion interference in the liquid-junction potential (provided chloride is the counter-ion), which is dependent on the composition and geometry of the bridge solution. The analytical interferences by sodium chloride are counteracted by the influence of ionic strength on magnesium ion activity and protein binding in the sample. In practice, the influence of sodium ion may be neglected (26, 27).

3.4.3 Influence of lipophilic anions This influence is due to transfer of lipophilic counter-ions, e.g., thiocyanates, from the sample into the Mg-ISE membrane. In principle it may violate the permselectivity condition, which is a prerequisite for proper functioning of all ISEs, and allows only cations to participate in the Mg-ISE potential formation. This influence has been observed in smoking individuals with high plasma thiocyanate concentration. If uncorrected, this influence will give falsely low results (28). The mechanism of this influence is different from that of calcium and sodium ions, and may result in prolonged malfunction of the Mg-ISE.

3.4.4 Influence of surfactants Calibrants that contain polyethylene oxide, e.g., Brij-35®, may exert an irreversible effect on the Mg-ISE via a similar mechanism to that described above for lipophilic anions. This effect may be less if alkyl-N-methylglucamide-based nonionic surfactants, e.g., MEGA 8®, are used instead (29).

3.4.5 Influence of proteins Proteins may affect the Mg-ISE, reversibly inducing a phenomenon called the asymmetry potential. Furthermore, protein adsorption at the Mg-ISE membrane may slow the response of the electrode. Such a change, if not compensated, will result in bias. The magnitude of this bias generally depends on ''distance from equilibrium'', which is a complex function of parameters. It may be decreased by increasing the Mg-ISE readout time (25).

3.4.6 Other influences Zinc-balanced heparin should not be used as anticoagulant because zinc can produce a significant positive bias in the determination of iMg (30) and related analytes such as ionized calcium (31) and total magnesium (32). In addition, influence by drugs, e.g., carbamazepine, has been reported (33).

3.5 pH adjustment

The concentration of iMg in plasma depends on pH, mainly because binding of magnesium to albumin increases with pH. For this reason the Mg-ISE system should measure pH simultaneously to allow adjustment to pH 7.4. A pH-adjusted result is useful if actual pH conditions cannot be maintained and is required for comparison with the reference interval of iMg.

The mechanism of pH dependence is similar to that for ionized calcium, but the effect is approximately half that for calcium (9, 34), i.e., a 2%–3% decrease in iMg per 0.1 increase in pH. The usable pH interval for correction is pH 7.0–7.8. Samples exceeding pH 7.8 should not be readjusted by, e.g., CO_2 changes or acidification, because of a risk of irreversible side reactions of magnesium ions (34).

In blood, the osmotic movement of water between plasma and erythrocytes adds to the pH effect by an approximately 0.7% increase in iMg per 0.1 pH decrease (35).

Complex binding of Mg^{2+} to bicarbonate and lactate and the residual liquid junction potential also depend on pH and the pH buffer value, because the concentration of corresponding anions of these salts changes with pH. The substance concentration of iMg changes less in plasma than in saline solution due to buffering of Mg^{2+}.

3.6 Donnan effect

The Donnan effect decreases the activity of cations in interstitial fluid relative to that of plasma. This explains the observed decrease in ionized calcium and iMg in some clinical settings (such as blood donation) in which an interstitial fluid of low cation activity replaces or has been added to plasma (36–38).

4. Reporting results

Determination of a true concentration of iMg would require knowledge and consideration of the concentrational activity coefficient (approx. 0.36; the exact value is unknown), the residual liquid junction potential (which causes a bias in plasma, when subtracted, of approx. –0.4 mV or –3%), and the mass concentration of water (which is 0.99 kg/L in the calibrator and 0.93 kg/L in normal plasma) (8). Since magnesium resembles calcium, there is a strong argument for using the same conventions for the reported value of iMg as for iCa (1). With the same conventions as for iCa, the reported value for iMg will be inaccurate by approximately +3% in comparison to the true concentration, i.e., the result would be 3% above the true value, but the exact value is not obtainable even for a ''standard'' plasma. The chemical potential or activity of iMg should be reported relative to the magnesium concentration in a simple protein-free calibrator of $I_m = 0.160$ mol/kg of magnesium chloride in physiological saline. The name of the quantity is the substance concentration of iMg in plasma analogous to iCa. Although a relative activity is measured, the reported quantity is a substance concentration with unit mmol/L, referring to the concentration of magnesium in the calibrator.

The determination of true molality would require that the activity coefficients in the calibrator and plasma, the residual liquid junction potential and the mass concentration of water in the calibrator (0.99 kg/L) be known and taken into account. With the same conventions as for iCa, the result would be inaccurate by approximately –4% in comparison to the true molality, i.e., the result would be 4% below the true value. Reporting of magnesium as molality is discouraged in clinical practice.

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