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Original Article

Pharmacokinetics of Magnesium Bolus Therapy in Cardiothoracic Surgery

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Objective: To investigate the pharmacokinetics of a 20 mmol magnesium bolus in regards to serum and urinary magnesium concentration, volume of distribution, and half-life.
Design: Prospective, experimental study.
Setting: A university-affiliated teaching hospital.
Participants: Twenty consecutive cardiac surgery patients treated with magnesium bolus therapy for prevention of arrhythmia.
Interventions: A 20-mmol bolus of magnesium sulfate was administered intravenously.
Measurements and Main Results: Median magnesium levels increased from 1.04 (interquartile range 0.94-1.23) mmol/L to 1.72 (1.57-2.14) mmol/L after 60 minutes of magnesium infusion ($p < 0.001$) but decreased to 1.27 (1.21-1.36) and 1.16 (1.11-1.21) mmol/L after 6 and 12 hours, respectively. Urinary magnesium concentration increased from 6.3 (4.2-14.5) mmol/L to 19.1 (7.4-34.5) mmol/L after 60 minutes ($p < 0.001$), followed by 22.7 (18.4-36.7) and 15 (8.4-19.7) mmol/L after 6 and 12 hours, respectively. Over the 12-hour observation period, the cumulative urinary magnesium excretion was 19.1 mmol (95.5% of the dose given). The median magnesium clearance was 10 (4.7-15.8) mL/min and increased to 14.9 (3.8-20.7; $p = 0.934$) mL/min at 60 minutes. The estimated volume of distribution was 0.31 (0.28-0.34) L/kg.
Conclusion: Magnesium bolus therapy after cardiac surgery leads to a significant but short-lived increase of magnesium serum concentration due to renal excretion and distribution, and the magnesium balance is neutral after 12 hours.

Key Words: intensive care; magnesium; pharmacokinetics; cardiac surgery; arrhythmia; atrial flutter

POSTOPERATIVE ARRHYTHMIAS may occur in up to 50% of cardiothoracic surgery patients[1–3] and are associated with increased mortality, morbidity, and length of stay.[4] Intravenous magnesium is commonly administered in the intensive care unit (ICU) to either prevent or treat arrhythmias in the postoperative course.[5]

Despite the widespread use of magnesium, evidence of prophylactic or therapeutic efficacy requires additional studies, as indicated by recent meta-analyses.[6–9] One of the difficulties in assessing the prophylactic or therapeutic efficacy of

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magnesium is the lack of a clear biochemical target. In particular, it is unclear whether the optimal target for intravenous magnesium supplementation in these patients should be the prevention of any hypomagnesemia or whether magnesium therapy should target mild or even moderate hypermagnesemia. To study such targets and their effect on arrhythmias, however, it is crucial to understand the pharmacokinetics of intravenous magnesium administration in cardiac surgery patients so that such targets can be achieved reliably. Although cardiothoracic surgery and intensive care management may influence pharmacokinetics due to perioperative intravenous fluids, transfusions, vasopressors, and critical illness, no study to date has examined the magnitude and duration of the effects of intravenous magnesium bolus therapy on serum magnesium levels and urinary magnesium excretion. As a consequence, currently there is no evidence-based, commonly used dosing regimen that reliably prevents hypomagnesaemia or ensures mild or moderate hypermagnesemia in these patients.

Accordingly, the authors aimed to assess serum and urine magnesium levels before and after the administration of a standardized dose of intravenous magnesium in cardiac surgery patients admitted to the ICU.

Methods

Study Inclusion Criteria

Inclusion criteria included (1) admission to the ICU after elective cardiac surgery and (2) a clinician's decision to administer intravenous magnesium. Exclusion criteria included (1) pre-existing or acute renal failure and (2) a serum magnesium level ≥ 1.5 mmol/L at baseline.

Austin Health Human Research Ethics Committee approval was attained on June 23, 2016 (reference number: LNR/15/Austin/306). All included patients gave written consent to participate in the study.

Participants

The study included 20 consecutive adult patients admitted to the ICU of the Austin Hospital (Victoria, Melbourne) after elective cardiac surgery.

Intervention

A 20 mmol bolus of magnesium sulfate (Hospira, Lake Forest, IL) was administered through a central venous catheter over 1 hour. Blood and spot urine samples were taken over a 12-hour period. The time points for measurements were immediately before, 60 minutes, 6 hours, and 12 hours after the magnesium infusion was initiated.

Primary Outcome

The primary outcome of this study was a change in the serum magnesium level over a 12-hour observation period. The rate of urinary magnesium excretion after the administration of a standardized dose of intravenous magnesium sulfate was the secondary outcome. Magnesium clearance was calculated based on the following formula:

$$K\ (\text{clearance}) = \text{urinary concentration} \times \text{urine flow} / \text{plasma concentration}.$$

Statistical Methods

Statistical analyses were performed using SPSS, Version 22.0 (IBM Corp, Armonk, NY). Continuous variables were expressed as median (interquartile range [IQR]), and categorical variables were expressed as number (%). Difference in measurements before and after drug administration was explored using paired t test or repeated measures analysis of variance. A 2-sided p value < 0.05 was considered to be statistically significant.

Results

The study included 20 patients admitted to a tertiary ICU from August 1 to 31, 2016. The baseline characteristics of included patients are shown in Table 1. All patients included gave written consent to participate in the study. No further magnesium boluses, oral or intravenous, were administered after the study medication.

Crystalloids (median 1,500 mL, IQR 1,000-2,625) were used for intraoperative management rather than colloid infusions (median 0). Isotonic cardioplegic solution (16 mmol/L of magnesium) during surgery amounted to a median of 4,236 mL (IQR 3,537-4,657). No diuretics were administered during surgery. Six patients received intraoperative magnesium, with doses ranging from 5 to 20 mg.

Effects on Magnesium

The serum magnesium concentration increased from a median of 1.04 (IQR 0.94-1.23) mmol/L before treatment to 1.72 (1.57-2.14) mmol/L after 60 minutes of magnesium infusion ($p < 0.001$), for a median increase of 0.75 (0.64-0.95) mmol/L after 1 hour, implying a median volume of distribution of 0.31 (0.28-0.34) L/kg, or 26.6 (21.1-31.2) L. However, the serum magnesium decreased to 1.27 (1.21-1.36) and 1.16 (1.11-1.21) mmol/L after 6 and 12 hours, respectively ($p < 0.001$ at both time points compared with the peak level at 60 minutes) (Table 2 and Fig 1). Moreover, the median half-life of magnesium was 3.01 (2.34-3.85) hours.

The urinary magnesium concentration increased from 6.3 (4.2-14.5) mmol/L before infusion to 19.1 (7.4-34.5) mmol/L after 60 minutes ($p < 0.001$), followed by 22.7 (18.4-36.7; $p = 0.813$ compared with the 60-min value) mmol/L and 15 (8.4-19.7, $p = 0.296$) mmol/L after 6 and 12 hours, respectively.

The median magnesium clearance was measured at 10 (4.7-15.8) mL/min before magnesium was administered and increased to 14.9 (3.8-20.7; $p = 0.934$) mL/min at 60 minutes, followed by 19.7 (14.9-25.1; $p = 0.566$) mL/min and 8.4 (5.9-15.8; $p = 0.989$) mL/min at 6 and 12 hours, respectively.

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