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Intravenous magnesium sulfate enhances the ability of dofetilide to successfully cardiovert atrial fibrillation or flutter: results of the Dofetilide and Intravenous Magnesium Evaluation

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Aims A previous study found that the adjunctive use of intravenous magnesium sulfate with ibutilide could increase the odds of a patient chemically cardioverting from atrial fibrillation (AF) or flutter (AFL) to normal sinus rhythm (NSR) by 78%. Whether or not intravenous magnesium has the same effect on dofetilide's ability to chemically cardiovert patients from AF/AFL to NSR is not known.

Methods and results This was a retrospective cohort evaluation of consecutive eligible patients receiving dofetilide for chemical cardioversion of AF or AFL at a single institution. All AF or AFL patients received dofetilide according to the institution's standard protocol, which required patients to remain as an inpatient for a minimum of 3 days or 6 doses after the initiation of dofetilide therapy. Patients receiving any dose of intravenous magnesium starting on the same day as dofetilide constituted the treatment group. Controls received dofetilide, but no intravenous magnesium any time prior to chemical cardioversion. Patients underwent continuous electrocardiographic monitoring throughout their hospital admission. Multivariable logistic regression analysis was used to determine the impact of intravenous magnesium on dofetilide's efficacy. A total of 160 patients in persistent AF or AFL (mean age 66.6 $\pm$ 11.0 years, 70.0% male, 30.0% in AF or AFL >15 days, 54.4% hypertension, 37.5% heart failure, 16.3% valvular disease, 16.3% previous myocardial infarction, and baseline serum magnesium levels 2.1 $\pm$ 0.26 mg/dL) and receiving dofetilide (mean dose 428 $\pm$ 118 μg/dose) were included in this analysis. The overall chemical cardioversion rate with dofetilide irrespective of adjunctive intravenous magnesium utilization was 41.9%. The concurrent administration of intravenous magnesium (n = 50) was associated with a 107% increased odds of successful chemical cardioversion [adjusted odds ratio: 2.07 (95% confidence intervals: 1.00–4.33)] compared with those who did not receive magnesium (n = 110). Only one case of torsade de pointes occurred in the no magnesium group during the index hospital admission.

Conclusion Concurrent use of intravenous magnesium is associated with an enhanced ability of dofetilide to successfully convert AF or AFL.

Keywords Dofetilide • Magnesium • Atrial fibrillation

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia.[1] It is the leading cause of embolic stroke and results in a two-fold increased mortality risk.[1] Dofetilide, an oral Vaughan Williams class III anti-arrhythmic agent that blocks the rapid component of the inward delayed rectifier potassium current (IKr), can chemically cardiovert up to 30% of patients with AF or atrial flutter (AFL) to normal sinus rhythm (NSR), but can also induce torsade de pointes (TdP) in ~0.8% of patients.[2]

In a recent meta-analysis,[3] intravenous magnesium prophylaxis was found to reduce patients' odds of developing post-cardiothoracic surgery AF by 66% ($P < 0.05$), demonstrating its innate anti-arrhythmic efficacy. As such, it could be hypothesized that intravenous magnesium might also enhance the efficacy of class III anti-arrhythmic drugs, such as dofetilide.

Moreover, in a recent retrospective analysis,[4] the impact of intravenous magnesium sulfate on the class III anti-arrhythmic ibutilide's ability to successfully convert patients with AF or AFL was evaluated. This cohort study found that among normo-magnesemic patients receiving magnesium prophylaxis, the adjusted odds of converting to NSR was 78% greater than those receiving ibutilide alone. Based upon these results, as well as for other potential indications such as TdP prevention,[4] normo-magnesemic patients at our institution sometimes receive intravenous magnesium in conjunction with class III anti-arrhythmic agents during chemical cardioversion of AF or AFL.

Thus, in this cohort evaluation, we sought to determine if concomitant intravenous magnesium sulfate prophylaxis in patients receiving dofetilide was an independent predictor of successful chemical cardioversion of chronic AF or AFL.

Methods

Design and population

This was a retrospective cohort evaluation of all normo-magnesemic patients who received dofetilide for acute chemical cardioversion of chronic AF or AFL at our institution between January 2000 and August 2008. All patients received dofetilide according to the institution's standard protocol, which required patients to remain as an inpatient for a minimum of 3 days or 6 doses after initiation of dofetilide therapy.[2] Patients receiving intravenous magnesium starting on the same day as dofetilide, but not for the treatment of TdP, constituted the treatment group. Controls received dofetilide, but no intravenous magnesium any time prior to chemical cardioversion. Patients were identified through pharmacy and billing records, and data were garnered from the medical records of eligible patients.

Trial endpoints and definitions

The primary endpoint evaluated was whether intravenous magnesium sulfate (at any dose) enhances the ability of dofetilide to successfully convert AF or AFL. Successful chemical cardioversion was defined as cardioversion to NSR prior to the use of direct current cardioversion or hospital discharge (documented by rhythm strip or cardiologist note). The impact of intravenous magnesium sulfate on the incidence of TdP (defined as sustained polymorphic ventricular tachycardia occurring any time during the index hospital admission and documented by rhythm strip or cardiologist note) was evaluated as a secondary endpoint.

Statistical analysis

Continuous variables are presented as means with standard deviations and are compared between groups using a Student's *t*-test or Mann–Whitney test (when appropriate). Dichotomous variables are presented as percentages and are compared between groups via χ^2 analysis or Fisher's exact test (where appropriate).

Given the observational study design utilized, important differences in observed demographic and pre- or peri-treatment variables were likely to occur which could bias the estimate of treatment effect. Therefore, we conducted multivariable logistic regression to control for potential confounders in our evaluation.

All of the variables in *Table 1* were included in the analysis. We first conducted univariate analysis to examine the association between the occurrences of the endpoint of interest (successful chemical cardioversion as the dependant variable) with our pre-, intra-, and post-treatment variables (independent variables). All variables with a *P*-value of ≤ 0.2 in the univariate analysis were entered into a multivariable logistic regression model. In the multivariable model, a *P*-value of ≤ 0.05 was considered significant. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated for all independent predictors. Statistical analysis was performed with SPSS version 15.0 (SPSS, Chicago, IL, USA).

Results

A total of 160 patients received dofetilide for the cardioversion of AF ($n = 150$) or AFL ($n = 10$) to NSR and met all other criteria for inclusion. Of the included patients, 110 patients did not receive intravenous magnesium sulfate and 50 patients received intravenous magnesium sulfate on the first day of dofetilide administration. The average first dose of magnesium was 3 ± 2 g and the total dose during the hospital course was 6 ± 5 g. Characteristics of the study population were similar between those with and without adjuvant magnesium sulfate (*Table 1*).

The overall dofetilide cardioversion rate was 41.9%. Forty-two out of 110 (38.2%) patients in the no magnesium cohort and 25 out of 50 (50.0%) patients in the magnesium cohort chemically converted to NSR. Intravenous magnesium enhanced the adjusted odds of successful cardioversion by 107% [AOR: 2.07 (95% CI: 1.00–4.33)]. No other independent predictors of successful cardioversion were identified upon multivariable analysis.

When evaluating the subgroups of patients with AF and AFL separately, magnesium was associated with an increased rate of chemical cardioversion in patients presenting with AF [AOR: 2.49 (95% CI: 1.14–5.46)] and AFL [AOR: 1.73 (95% CI: 0.88–3.38)], although the later failed to reach statistical significance ($P = 0.11$).

Only one case of TdP occurred (in the no magnesium group) during the index hospital admission.

Discussion

Many studies[3,5–8] have shown an innate atrial anti-arrhythmic benefit associated with intravenous magnesium; however, this current cohort study is the first to evaluate the impact of concomitant intravenous magnesium administration on dofetilide's

Table 1 Patient characteristics

Variable	Total cohort (*N* = 160) [*n* (%)]	Magnesium (*N* = 50) [*n* (%)]	No magnesium (*N* = 110) [*n* (%)]	*P*-value
Atrial fibrillation	150 (93.8)	46 (92.0)	104 (94.5)	0.29
Age (mean ± SD)	66.6 ± 11.0	66.4 ± 11.8	66.7 ± 10.6	0.87
Age >65 years	83 (51.9)	25 (50.0)	58 (53.2)	0.71
Gender (male)	115 (71.9)	38 (76.0)	77 (70.0)	0.43
AF or AFL > 15 days duration	48 (30.0)	15 (30.0)	33 (30.0)	>0.99
History of hypertension	87 (54.4)	28 (56.0)	59 (53.6)	0.78
History of smoking	27 (16.9)	10 (20.0)	17 (15.5)	0.47
History of myocardial infarction	26 (16.3)	7 (14.0)	19 (17.3)	0.60
Family history of CAD	48 (30.0)	16 (32.0)	32 (29.1)	0.71
History of high cholesterol	49 (30.6)	20 (40.0)	29 (26.4)	0.08
History of heart failure	60 (37.5)	23 (46.0)	37 (33.6)	0.13
EF (%) (mean ± SD)	36.1 ± 17.5	37.9 ± 16.0	35.1 ± 18.7	0.49
Baseline QTc (ms) (mean ± SD)	426.0 ± 40.8	427.8 ± 42.7	425.2 ± 40.0	0.71
Maximum post-dofetilide QTc (ms) (mean ± SD)	468.2 ± 46.2	464.3 ± 50.7	470.1 ± 43.9	0.48
Baseline serum magnesium (mg/dL) (mean ± SD)	2.1 ± 0.3	2.0 ± 0.3	2.1 ± 0.2	0.45
Baseline serum creatinine (mg/dL) (mean ± SD)	1.0 ± 0.5	1.1 ± 0.7	1.0 ± 0.3	0.23
Dofetilide dose (mg per dose) (mean ± SD)	0.429 ± 0.118	0.418 ± 0.128	0.433 ± 0.114	0.43
History of diabetes mellitus	21 (13.1)	6 (12.0)	15 (13.6)	0.78
History of cerebrovascular disease	6 (3.8)	2 (4.0)	4 (3.6)	0.91
History of valve disease	26 (16.3)	9 (18.0)	17 (15.5)	0.69
Medical therapy at admission				
β-Blocker	133 (83.1)	45 (90.0)	88 (80.0)	0.12
CCB	47 (29.4)	14 (28.0)	33 (30.0)	0.80
Digoxin	67 (41.9)	26 (52.0)	41 (37.3)	0.08
Statin	76 (47.5)	21 (42.0)	55 (50.0)	0.35
ACE inhibitor/ARB	99 (61.9)	33 (66.0)	66 (60.0)	0.47
Aspirin	38 (23.8)	12 (24.0)	26 (23.6)	0.96
Warfarin	156 (97.5)	50 (100)	106 (97.2)	0.24
Diuretics	76 (47.5)	24 (48.0)	52 (47.3)	0.93
Corticosteroids	9 (5.6)	4 (8.0)	5 (4.5)	0.38
NSAIDs	10 (6.3)	2 (4.0)	8 (7.3)	0.43
Prior anti-arrhythmic therapy				
Sotalol	29 (18.1)	10 (20.0)	19 (17.3)	0.68
Amiodarone	31 (19.4)	8 (16.0)	23 (20.9)	0.47

AF, atrial fibrillation; AFL, atrial flutter; CAD, coronary artery disease; EF, ejection fraction; CCB, calcium channel blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDs, non-steroidal anti-inflammatory drugs.

efficacy. Our cohort study, utilizing patients undergoing chemical cardioversion, found that prophylactic use of intravenous magnesium sulfate was in fact an independent predictor of successful cardioversion among AF or AFL patients given dofetilide, increasing the odds of cardioversion by over two-fold.

Interestingly, the 107% increased odds of cardioversion seen with intravenous magnesium in this study is higher than the 78% improvement observed in the most recent Treatment with Ibutilide and Magnesium Evaluation (TIME). The exact reason for differences in magnesium's effect is unknown, but could be a result of the greater mean intravenous magnesium dose used at the initial time of class III anti-arrhythmic administration in this analysis compared with the previous ibutilide analysis (only about one-third of patients received the most efficacious 4 g dose in TIME), a differential ability of magnesium to enhance the efficacy of dofetilide and ibutilide, or the difference could be due to random chance (suggested by the fact that the 95% CI of both studies significantly overlap).

In addition to being clinically relevant, it is likely that the use of intravenous magnesium in conjunction with dofetilide or ibutilide is also economically advantageous. A previous pharmacoeconomic analysis[9] demonstrated that the total costs per patient was lower in the ibutilide plus magnesium group compared with ibutilide alone (US$1075 vs. US$1201 in 2004) and, upon non-parametric bootstrapping, that an initial ibutilide plus magnesium strategy to cardiovert patients from AF or AFL would result in both lower costs and greater efficacy 93.4% of the time.

There are some limitations to our study that should be noted. First, as this is an observational study, we can only say there is an association between intravenous magnesium administration and the increased cardioversion rate with dofetilide. A randomized controlled trial would be required to prove causality. In addition, although we have strongly suggested potential benefits with intravenous magnesium, we cannot determine the mechanism of its benefit from this study. Magnesium's benefits may be related to its role in accentuating intracellular potassium concentrations by blocking the IKr potassium channel; through its ability to regulate intracellular calcium concentrations via the inhibition of calcium influx through L-type calcium channels or by directly opposing calcium's intracellular actions; or a combination of these two mechanisms.[10–12] Finally, although TIME[4] was able to demonstrate a dose–response relationship between intravenous magnesium dose and improvements in cardioversion rate with ibutilide, this study did not have adequate numbers of patients receiving different magnesium doses to conduct a similar analysis with dofetilide. We were also unable to determine the optimal intravenous magnesium dosing regimen, although our data suggest that starting on Day 1 of dofetilide therapy is reasonable.

Conclusion

Intravenous magnesium sulfate is an independent predictor of successful chemical cardioversion among a population of patients receiving dofetilide. A randomized controlled trial should be conducted to confirm these findings.

Conflict of interest: none declared.

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