ORIGINAL ARTICLE

Rapid pharmacological cardioversion of recent-onset atrial fibrillation using antazoline in elderly patients

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KEY WORDS

antazoline, atrial fibrillation, elderly, pharmacological cardioversion

ABSTRACT

INTRODUCTION There is insufficient evidence on the efficacy and safety of pharmacological cardioversion of recent-onset atrial fibrillation (AF) in elderly patients. Antazoline has been shown to be effective and safe in various patient populations.

OBJECTIVES We aimed to compare the clinical efficacy and safety of intravenous antazoline for pharmacological cardioversion of recent-onset AF between patients aged 75 years or older and those younger than 75 years.

PATIENTS AND METHODS This retrospective analysis was conducted using data derived from emergency room medical records of patients referred for pharmacological cardioversion due to symptomatic AF lasting less than 48 hours. The threshold for old age was set at 75 years. Conversion to sinus rhythm was considered the primary efficacy outcome. The primary safety outcome was defined as any adverse event requiring hospitalization.

RESULTS The study included 334 participants, of whom 110 patients were aged 75 years or older (study group) and 224 patients were younger than 75 years (controls). Successful cardioversion was achieved using lower mean (SD) antazoline doses in the study group than in controls: 151 (59) mg vs 168 (58) mg ($P = 0.039$). Study and control groups showed a similar efficacy and safety of antazoline (78.2% and 68.3%, respectively; odds ratio [OR], 1.66; 95% CI, 0.98–1.31; $P = 0.06$) as well as hospitalization rates (0.9% and 4.0%, respectively; OR, 0.22; 95% CI, 0.03–1.75; $P = 0.17$).

CONCLUSIONS Intravenous antazoline seems to be effective and safe for pharmacological cardioversion of recent-onset AF in elderly patients in the emergency setting.

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INTRODUCTION The prevalence of atrial fibrillation (AF) is higher in elderly patients than in younger individuals.[1,2] As patients aged 75 years or older are at high risk of thromboembolic complications, they should be systematically screened for AF to establish a timely diagnosis.[1] While the decision on initiating oral anticoagulation in elderly patients is rather straightforward, less is known about the optimal long-term strategy for rhythm or rate control.[1] The presence of such risk factors as frailty and multimorbidity results in a more common use of the rate control strategy in this population.[1,3-5] The major concerns raised in relation to standard rhythm control therapies include their lower effectiveness and a higher risk of complications.[1] Even less is known about the optimal drug use for pharmacological cardioversion of AF. Owing to a relatively high prevalence of coronary artery disease (CAD) and heart failure (HF) in the elderly, amiodarone may be the most suitable agent in this setting, but definitive clinical data are lacking.[1] On the other hand, the slow-acting amiodarone may not be the most viable option for rapid cardioversion in the emergency department (ED).[6] Antazoline is an antihistaminic drug with potent

WHAT'S NEW?

Our study revealed similar efficacy and safety of intravenous antazoline in patients aged 75 or older and those younger than 75 years in terms of conversion to sinus rhythm and risk of hospitalization due to adverse events. Therefore, antazoline may be a viable option for pharmacological cardioversion of recent-onset atrial fibrillation in elderly patients in the emergency setting if other fast-acting agents are contraindicated or not available.

antiarrhythmic properties and a rapid onset of action when administered intravenously.[7-9] However, its exact antiarrhythmic mechanism of action remains unclear. Recent research has implied a multifactorial mode of action involving the sodium and potassium channels. Animal model studies reported a significant prolongation of atrial and ventricular effective refractory periods leading to a remarkable increase in atrial and ventricular postrepolarization refractoriness, an antiarrhythmic mechanism observed for amiodarone or quinidine.[8,10-12] Antazoline was tested in various cohorts presenting with recent-onset AF and was found to be effective and safe even in patients with stable CAD or postmyocardial infarction.[13-15] However, intravenous antazoline may reduce cardiac output or blood pressure and exacerbate stable HF.[9,12,16] Nevertheless, its pharmacokinetic properties seem to be favorable, with a rapid decline in plasma concentrations, terminal elimination half-life of 2.29 hours, mean residence time of 3.45 hours, and clearance of 80.5 l/h.[17]

The aim of this study was to compare the clinical efficacy and safety of intravenous antazoline for pharmacological cardioversion of recent-onset AF between patients aged 75 years or older and those younger than 75 years.

PATIENTS AND METHODS This was a retrospective analysis of data from ED medical records of a tertiary care cardiological center for the years 2008 to 2012. The single inclusion criterion for this study was pharmacological cardioversion using intravenous antazoline for the treatment of a symptomatic AF episode lasting less than 48 hours. Patients who did not receive antazoline were excluded from the study. Data on patient characteristics, medication use, and the outcomes of treatment were collected anonymously. Comorbidities were evaluated based on medical history and available patient records. The primary efficacy outcome was defined as successful conversion to sinus rhythm confirmed by 12-lead electrocardiography. The primary safety outcome was defined as any adverse event leading to hospitalization. Other outcomes of interest included hospital discharge, hospitalization due to unsuccessful cardioversion of AF, systolic blood pressure of less than 100 mm Hg, or bradyarrhythmia (heart rate <60 bpm).

The ED physician on site was responsible for all clinical decisions, including a referral for cardioversion, drug administration, discharge or referral for hospitalization, among others. Patients were referred for pharmacological cardioversion of symptomatic AF according to standard clinical guidelines.[1] Asymptomatic patients were not considered for immediate cardioversion and were referred either to an outpatient clinic or to a hospital for further evaluation. The background antiarrhythmic therapy was not discontinued and did not affect the decision on or the timing of cardioversion in the ED.

In accordance with a clinical standard in our center, antazoline was administered intravenously under continuous cardiac monitoring in divided doses of 50 mg every 3 to 5 minutes up to a maximum dose of 250 to 300 mg or until conversion to sinus rhythm was achieved.[14,16] Any other concomitant medications, including intravenous metoprolol, ion solutions, and intravenous propafenone, were administered at the discretion of the ED physician. Patients who were eligible for intravenous amiodarone or electrical cardioversion (eg, presented with hemodynamic instability) were generally admitted to the cardiology ward and therefore were excluded from this analysis. Although indicated by clinical guidelines for rapid pharmacological cardioversion, flecainide and procainamide are currently unavailable in Poland.[1]

The globally accepted threshold for old age is 65 years, and the available literature on rhythm control in elderly patients generally reports on populations aged over 65 or 70 years.[3-5] While the mean age of patients in our previous studies on antazoline was almost 70 years, for the purpose of the current analysis, we adopted the threshold of 75 years.[9,14,16] This threshold is consistent with the age criterion for active monitoring for AF in clinical guidelines as well as with recent studies on oral anticoagulation in elderly patients.[1,18] Thus, participants were divided into a study group including patients aged 75 years or older and a control group including patients younger than 75 years.

The analysis was approved by the local Bioethics Committee (no. IK-NP-0021-74/1529/15 issued on October 5, 2015). Due to the retrospective design of the study, patients' consent was not required.

Statistical analysis Continuous variables were compared between the 2 groups using the *t* test for normally distributed data (the normal distribution of all continuous variables was explored by examined skewness), and the results were presented as mean (SD). Categorical variables were compared between the 2 groups using the χ^2 test or the Fisher exact test in cases of a minimum expected count of less than 5. The results were reported as the absolute numbers and percentages. Cochran–Mantel–Haenszel modified ridit scores using the row mean score *P* value were applied for non–time-to-event ordinal variables (atrioventricular block). An odds ratio (OR) with 95% CI was calculated. Univariable and backward

TABLE 1 Baseline characteristics of patients aged 75 years or older and those younger than 75 years undergoing cardioversion of atrial fibrillation with antazoline

Parameter	Patients aged ≥75 years (n = 110)	Patients aged <75 years (n = 224)	*P* value
Age, mean (SD)	78.9 (3.6)	63.7 (7.8)	<0.001
Male sex	69 (62.7)	154 (68.7)	0.27
Comorbidities			
CAD	64 (58.2)	74 (33.0)	<0.001
Previous PCI	16 (14.5)	31 (13.8)	0.86
Previous CABG	31 (28.2)	22 (9.8)	<0.001
Hypertension	72 (65.4)	130 (58.0)	0.19
Diabetes mellitus	15 (13.6)	43 (19.2)	0.21
Thyroid disorders	13 (11.8)	16 (7.1)	0.15
Structural heart disease			
None	98 (89.1)	164 (73.2)	0.004
Ischemic	12 (10.9)	54 (24.1)	
Nonischemic	0	3 (1.3)	
Valvular	0	3 (1.3)	
Cardiac implantable electronic device			
None	88 (80.0)	187 (83.5)	0.37
Pacemaker	20 (18.2)	36 (16.1)	
ICD	0	0	
CRT	2 (1.8)	1 (0.4)	
Concomitant arrhythmia			
Atrial flutter	7 (6.4)	33 (14.7)	0.027
Atrial tachycardia	2 (1.8)	9 (4.0)	0.35
PVC	10 (9.1)	5 (2.2)	0.009
Sick sinus syndrome	26 (23.6)	42 (18.7)	0.3
First-degree AV block	5 (4.5)	1 (0.4)	0.036
Second-degree AV block	2 (1.8)	2 (0.9)	
Third-degree AV block	0	2 (0.9)	
Chronic antiarrhythmic therapy			
Propafenone	8 (7.3)	24 (10.7)	0.61
Amiodarone	2 (1.8)	12 (5.4)	0.17
Sotalol	2 (1.8)	13 (5.8)	0.16
Any antiarrhythmic drug	12 (10.9)	42 (18.8)	0.07

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: AV, atrioventricular; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention; PVC, premature ventricular contraction

TABLE 2 Differences in antazoline dose for successful and failed cardioversions between patients aged 75 years or older and those younger than 75 years

Parameter		Patients aged ≥75 years (n = 102)	Patients aged <75 years (n = 208)	*P* value
Antazoline dose, mg	Successful cardioversion	151 (59)	168 (58)	0.04
	Failed cardioversion	176 (74)	201 (70)	0.14
P value		*P* = 0.09	*P* <0.001	

Data are presented as mean (SD)

multivariable logistic regression analyses were performed to establish the relationship between patient characteristics (independent variables) and successful cardioversion (dependent variable). The initial model included all factors listed in TABLE 1. A 2-way interaction between sex, age (≥75 vs <75 years), and other factors was tested. Explanatory categorical variables with multiple levels (k >2) were recorded on k – 1 dummy indicators (atrioventricular block). Zero-one coding was used. A significance level of 0.05 was required for a variable to stay in the model. In the case of a zero number of events in one of the groups, the ORs were calculated using the Firth penalized likelihood approach. The goodness of fit of the final model was assessed using the area under the receiver operating characteristic curve (*C* statistics) with 95% CI. All of the hypotheses were 2-tailed with type I error of 0.05. The statistical analysis was conducted using the SAS statistical software version 9.4 (SAS Institute Inc, Cary, North Carolina, United States).

RESULTS Of the 548 consecutive patients undergoing pharmacological cardioversion of recent-onset AF, 334 received at least 1 dose of antazoline and were included in the study. There were 110 patients aged 75 years or older (study group) and 224 patients younger than 75 years who served as controls. The baseline characteristics of the study group and controls are summarized in TABLE 1. As expected, patients in the study group were significantly older but also had a higher risk of CAD and coexisting ventricular arrhythmia. On the other hand, the risk of a structural heart disease (SHD) or concomitant atrial flutter was significantly higher in the control group.

Mean antazoline doses for successful and failed cardioversions in the study and control groups are presented in TABLE 2. The mean antazoline dose in the study group was 156.4 (63.1) mg vs 178.6 (64.2) mg in controls (*P* = 0.004). The effective antazoline dose was significantly lower in the study group than in the control group.

The clinical outcomes of the study are presented in TABLE 3. There was no significant difference in the clinical efficacy and safety of antazoline between the study and control groups. Additional analyses revealed a higher efficacy of antazoline in men aged 75 years or older vs men younger than 75 years (Supplementary material, *Tables S1–S4*). In the univariable and multivariable analyses, age, chronic antiarrhythmic therapy, SHD, and male sex were not predictors of successful cardioversion (Supplementary material, *Tables S5* and *S6*). There was a strong interaction between sex and CAD in terms of successful cardioversion. Among men, the efficacy of antazoline in the group with CAD was 3.9-fold higher than in the group without CAD (95% CI, 2.02–7.51). However, no such association was found for women (OR, 0.95; 95% CI, 0.36–2.49). Previous atrial tachycardia was the predictor of cardioversion failure (OR, 0.198; 95% CI, 0.051–0.779).

TABLE 3 Efficacy and safety of antazoline in patients aged 75 years or older and those younger than 75 years

Parameter	Patients aged ≥75 years (n = 110)	Patients aged <75 years (n = 224)	OR (95% CI)	*P* value
Conversion to sinus rhythm	86 (78.2)	153 (68.3)	1.66 (0.98–1.31)	0.06
Discharge	93 (84.5)	180 (80.7)	1.34 (0.72–2.47)	0.35
Hospitalization for AF	16 (14.7)	40 (17.4)	0.78 (0.42–1.47)	0.45
Hospitalization for AEs	1 (0.9)	9 (4.0)	0.22 (0.03–1.75)	0.17
Hospitalization (other)	4 (3.6)	2 (0.9)	4.19 (0.76–23.2)	0.09
SBP <100 mm Hg	2 (1.8)	4 (1.8)	1.02 (0.18–5.65)	1.00
Bradyarrhythmia	10 (9.1)	22 (9.8)	0.92 (0.42–2.01)	0.83

Data are presented as number (percentage).

Abbreviations: AE, adverse event; AF, atrial fibrillation; OR, odds ratio; SBP, systolic blood pressure

DISCUSSION The main finding of the study is the similar efficacy and safety of antazoline in elderly (≥75 years) and younger (<75 years) patients undergoing pharmacological cardioversion of recent-onset AF in the ED setting. This adds to the available evidence that antazoline can be a viable option for cardioversion in various patients, including those with several comorbidities and those at older age.

The mean age of our study group was almost 80 years vs 64 years in controls. As expected, CAD was more prevalent in the older group, while surprisingly, younger patients more often presented with SHD. For the purpose of this study, SHD was defined as a history of myocardial infarction or any other previously diagnosed nonischemic cardiomyopathy, both of which are well-recognized risk factors for poor long-term prognosis. Therefore, it is possible that our group of elderly patients (≥75 years) included those who lived longer with stable CAD and not those who died earlier due to HF. In our study, CAD and SHD were reported in 58% and 11% of patients, respectively, and both these conditions are well-known contraindications to the use of class IC antiarrhythmic drugs for rapid cardioversion.[1]

Our study revealed a trend for a higher efficacy of antazoline in patients aged 75 years or older. However, this was not confirmed in the logistic regression analysis, contrary to the history of CAD. This observation is in line with our previous research.[14] The reason for the higher efficacy of antazoline in men with CAD has not been fully elucidated. There was no significant difference between men with and without CAD in terms of chronic antiarrhythmic therapy, but the medical records lacked information on the use of other chronic therapies. No reliable data were also reported in the AnPAF (Antazoline in Rapid Conversion of Paroxysmal Atrial Fibrillation) or CANT (Cardioversion With Antazoline Mesylate) studies.[9,15]

In our previous study on the general efficacy of antazoline, cardioversion was successful in 71.6% of the cases in the population with a mean (SD) age of 68.8 (9.8) years.[16] In a slightly older population with CAD (mean [SD] age, 71.3 [9.1] years), the conversion rate reached 82.6% and was significantly higher than in patients without CAD.[14] Recently, Wybraniec et al[15] reported an even higher efficacy of antazoline (85.3%), although in a slightly younger population (mean [SD] age, 65.5 [11.9] years).[15] In our study, the effective dose of antazoline was significantly lower in patients aged 75 years or older than in controls, but the reason for this remains unclear. Even more interestingly, although the target dose specified in the Methods section was higher, the mean (SD) maximum dose of antazoline administered in patients aged 75 years or older was 176 (74) mg despite failed cardioversion. This can probably be explained by the physician's reluctance to escalate the dose of antazoline to avoid potential adverse events.

The high efficacy of antazoline in patients aged 75 years or older does not appear to compromise its safety because only 1 patient in this group was hospitalized due to adverse events. However, a direct comparison with other clinical studies is difficult; for example, the CANT study did not report on any safety end points despite enrolling as many as 289 patients.[15] In a study on patients undergoing pulmonary vein isolation, Balsam et al[13] described 7 cases of antazoline discontinuation: nausea in 3 patients, right bundle branch block in 2 patients, as well as single cases of nonsustained ventricular tachycardia and hypotension. A single case of HF exacerbation reported in the AnPAF trial was resolved with intravenous diuretics.[9] The safety of antazoline was also reported in stable patients with a history of myocardial infarction, where only 1 of the 65 patients (1.6%) undergoing cardioversion required hospitalization due to an adverse event.[14]

The results of the AnPAF trial were included in a Bayesian network meta-analysis to indirectly compare different antiarrhythmic agents used for pharmacological cardioversion of recent-onset AF in the ED setting.[19] The calculated OR for antazoline was 24.9 (95% CI, 7.4–107.8), which was markedly higher than that for propafenone, flecainide, or vernakalant. Propafenone or flecainide administration may be significantly limited in older patients due to an increased risk of CAD—a well-known contraindication to the use of class IC antiarrhythmic drugs.[1] In our analysis, patients with CAD constituted almost 60%

of the study group. While amiodarone is considered to be the safest drug for pharmacological cardioversion of AF, its slow onset of action and significantly lower efficacy vs antazoline limit its use as the optimal treatment in the ED setting.[1,6,15] Vernakalant is not available in Poland due to high cost.

In our study, oral anticoagulation was not systematically assessed, but none of the patients underwent transesophageal echocardiography (TEE). The role of TEE is different in the setting of recent-onset vs persistent AF.[1,20-22] In patients with a very low risk of stroke and AF lasting less than 48 hours, TEE was reported to be used in a minority of cases.[21] This is in contrast to the setting of elective cardioversion of persistent AF, where TEE seems to be performed in most cases, particularly in high-volume or university centers. A history of thromboembolism, multiple comorbidities, and uncertainty as to oral anticoagulation are among the most important factors favoring the use of TEE before cardioversion.

Our study has several limitations inherent to the retrospective design, including potential selection bias, the risk of selective reporting, and the lack of important data, such as the time to conversion or overall time spent in the ED. To overcome these limitations, we enrolled consecutive patients, extracted all the available data from the medical records, and included all patients who were administered at least 1 dose of antazoline regardless of any other treatment received. Finally, as this study was designed to assess patients in the ED setting, there was no follow-up after hospital discharge or referral for hospitalization.

In conclusion, intravenous antazoline seems to be equally effective and safe for pharmacological cardioversion of recent-onset AF in elderly patients (≥75 years) as in younger patients (<75 years) in the emergency setting.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT MMF and AM conceived the concept of the study and designed the research. MMF, AM, and MZ collected the raw data. IK performed the statistical analysis. All authors were involved in the interpretation of the results. MMF prepared the manuscript draft. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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