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Original Article

Systematic review of the safety and efficacy of antazoline in the treatment of atrial fibrillation

[Revisión sistemática de la seguridad y eficacia de la antazolina en el tratamiento de la fibrilación auricular]

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Abstract

Context: In the emergency department, patients with recent-onset atrial fibrillation are typically managed with intravenous antiarrhythmic agents. However, the currently used agents have a low efficacy and safety profile. Antazoline is an antihistaminic agent that has been shown to have a strong antiarrhythmic effect when administered intravenously, facilitating rapid conversion to normal sinus rhythm.

Aims: To systematically review the literature on the safety and efficacy of antazoline in the treatment of recent-onset short-duration atrial fibrillation and to compare the clinical efficacy of antazoline to that of other antiarrhythmic agents listed in clinical guidelines.

Methods: The study was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. A comprehensive search of databases (PubMed, Scopus, ScienceDirect, Web of Sciences, Google Scholar, Clinical trial.gov) for relevant studies in English from inception to 2021 using keywords involving "antazoline" AND other terms such as "antiarrhythmic", "atrial fibrillation", and "arrhythmia".

Results: Of the 478 studies identified, 446 were screened, and 7 were included, one of which was a randomized control trial, and the others were observational studies. The majority of studies indicated that antazoline resulted in rapid cardioversion to sinus rhythm. When compared to other pharmacological cardioversion options, antazoline achieved higher cardioversion rates than amiodarone or propafenone and was generally a safer option.

Conclusions: Antazoline appears to be an effective pharmacological agent for the rapid cardioversion of short-term atrial fibrillation. More randomized clinical trials, however, should be conducted to strengthen the evidence.

Keywords: antazoline; efficacy; pharmacological cardioversion; recent-onset atrial fibrillation; safety.

Resumen

Contexto: En el departamento de emergencias, los pacientes con fibrilación auricular de inicio reciente generalmente se tratan con antiarrítmicos intravenosos. Sin embargo, los agentes utilizados actualmente tienen un perfil de eficacia y seguridad bajo. La antazolina es antihistamínico que ha demostrado tener un fuerte efecto antiarrítmico cuando se administra por vía intravenosa, lo que facilita la rápida conversión al ritmo sinusal normal.

Objetivos: Revisar sistemáticamente la literatura sobre la seguridad y eficacia de la antazolina en el tratamiento de la fibrilación auricular de corta duración de aparición reciente y comparar la eficacia clínica de la antazolina con la de otros agentes antiarrítmicos enumerados en las guías clínicas.

Métodos: El estudio se redactó de acuerdo con el protocolo *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA). Se realizó una búsqueda exhaustiva en bases de datos (PubMed, Scopus, ScienceDirect, Web of Sciences, Google Scholar, Clinical trial.gov) de estudios relevantes en inglés, desde el inicio hasta 2021, utilizando palabras clave que incluyeron "*antazoline*" *AND* otros términos como ""*antiarrhythmic*", "*atrial fibrillation*" y "*arrhythmia*".

Resultados: De los 478 estudios identificados, 446 fueron evaluados y se incluyeron 7, uno de los cuales fue un ensayo de control aleatorio y los otros fueron estudios observacionales. La mayoría de los estudios indicaron que la antazolina produjo una cardioversión rápida al ritmo sinusal. En comparación con otras opciones de cardioversión farmacológica, la antazolina logró tasas de cardioversión más altas que la amiodarona o la propafenona y, en general, fue una opción más segura.

Conclusiones: La antazolina parece ser un agente farmacológico eficaz para la cardioversión rápida de la fibrilación auricular a corto plazo. Sin embargo, se deben realizar más ensayos clínicos aleatorios para fortalecer la evidencia.

Palabras Clave: antazolina; eficacia; cardioversión farmacológica; fibrilación auricular de inicio reciente; seguridad.

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INTRODUCTION

Atrial fibrillation (AF), the most common form of sustained cardiac arrhythmia among the general population, has grown to epidemic proportions (Schnabel et al., 2015). The global prevalence of AF was estimated to be around 26 million in 2016, with the number expected to double over the next 50 years (Benjamin et al., 2019).

The prevalence of AF varies according to demographic factors such as age, gender, ethnicity, and region. It is estimated that AF affects 1-2% of the general population in the United States and Europe. The prevalence of AF increases with age, reaching nearly 8 times at age 80 to 89 years (Lip et al., 2012). According to community-based studies, males are more susceptible to the development of AF than females. However, since females live longer than males, both have a comparable cumulative lifetime risk of AF at about 30% (Magnussen et al., 2017; Pothineni and Vallurupalli, 2018). Several studies have found racial differences in AF burden and incidence. A multiethnic study of AF incidence in the UK Clinical Practice Research Datalink from 2001 to 2013 discovered that AF was lowest among blacks (4.6)/1000 persons/year and Asians (5.4)/1000 compared to (8.1)/1000 whites (Martinez et al., 2015).

AF is characterized by rapid, irregular atrial excitations that result in dyssynchronous and ineffectual atrial contractions, which affect ventricular contractions and cardiac output (Staerk et al., 2017). It has been recognized as a significant cause of death and a risk factor for a variety of cardiovascular diseases, including stroke, heart failure, and sudden cardiac death(Ang et al., 2020). AF can occur on its own or in conjunction with other types of supraventricular arrhythmias such as atrial flutter. The latter is distinguished by a rapid coordinated rhythm that can progress into AF later on (Fuster et al., 2006).

The current approach to AF management is directed toward preventing complications and ameliorating symptoms. Depending on the patient's condition, AF is managed with either rate control or rhythm control agents. Anticoagulants are frequently administered to patients in order to reduce the risk of thromboembolism and improve survival (Fuster et al., 2006; Ma et al., 2020). Electrical cardioversion (CV) can be used to restore normal sinus rhythm (SN), and it is generally thought to be more effective than drug therapy. However, general or local anesthesia is required, and the patient must fast for at least 6 h prior to the procedure. Pharmacological cardioversion on the other hand, does not require sedation and is associated with a lower risk of complications (Hanley et al., 2016). It is achieved by administering Intravenous antiarrhythmic agents such as ibutilide, flecainide, dofetilide, propafenone and amiodarone. These agents are limited by their modest efficacy, potential proarrhythmic effect, delayed cardioversion time, and other non-cardiac side effects such as hypotension (Camm et al., 2010).

As a result, efforts were focused on developing safe and selective pharmacological agents capable of rapidly cardioverting AF to normal SN. Indeed, recent antiarrhythmic drugs have primarily targeted atrial-specific ion channels implicated in AF in order to reduce ventricular proarrhythmia (Zimetbaum, 2012).

Antazoline is a first-generation antihistaminic agent with quinidine-like properties and antiarrhythmic activity that was first described by Dutta et al. (1949). Several reports on the intravenous use of antazoline against ventricular and supraventricular arrhythmias have been published since then (Dreifus et al., 1963; Kehler and Gehring, 1970; Reynolds Jr et al., 1964). Downar and Waxman (1975) demonstrated the successful use of intravenous antazoline in seven patients who failed to respond to common antiarrhythmic drugs such as quinidine and procainamide. Previous studies suggested that antazoline achieved higher cardioversion rates when used to manage paroxysmal AF than chronic AF (Balsam et al., 2015). Until now, the published randomized controlled trials (RCTs) on the antiarrhythmic activity of antazoline are lacking and the drug is not formally listed in the relevant guidelines. However, in Poland, antazoline has been approved and marketed for the rapid termination of short-duration AF in the emergency department due to its rapid onset of action within minutes of intravenous administration (Palimonka et al., 2020).

The purpose of this study is to review and evaluate the literature on the efficacy and safety profile of antazoline in the rapid cardioversion of short-duration AF to SN.

MATERIAL AND METHODS

Study protocol

The PRISMA protocol was adopted to guide the authors through the process of reviewing the literature and summarizing papers (Fig. 1).

Development of research question and systemic searching strategies

Previous research was used to develop the study's research question (Dreifus et al., 1963; Kehler and Gehring, 1970; Reynolds Jr et al., 1964). PICO, a tool used in evidence-based clinical practice, guided the process of developing the research question. Adapted from Mohamed Shaffril et al. (2021), this method described four major concepts: population, intervention, control, and outcomes. In our study, the following aspects were identified: patients with short-duration recent-onset AF (population), intravenous antazoline (intervention), other intravenous antiarrhythmic agents or placebo (control), conversion to normal SN, safety, and efficacy (outcome). Based on these considerations, the following research question was developed for this study: When compared to other pharmacological agents, is antazoline a safe and effective agent for the treatment of recent-onset short-duration AF?

Literature identification and screening

A comprehensive literature search was conducted on the following databases: PubMed, ScienceDirect, Google Scholar, Scopus, Web of Sciences, and Clinical trial.gov for relevant studies up to 2021. The language of search was restricted to English and the following search keywords and phrases were used: 'antazoline', 'antiarrhythmic', 'atrial fibrillation', 'arrhythmia'. RCTs and observational studies (prospective/retrospective) involving the use of intravenous antazoline for cardioversion of recent-onset AF were eligible. The clinical trial registry websites (https://clinicaltrials.gov/) and (http://controlled-trials.com) were used to screen the literature on published and unpublished clinical trials.

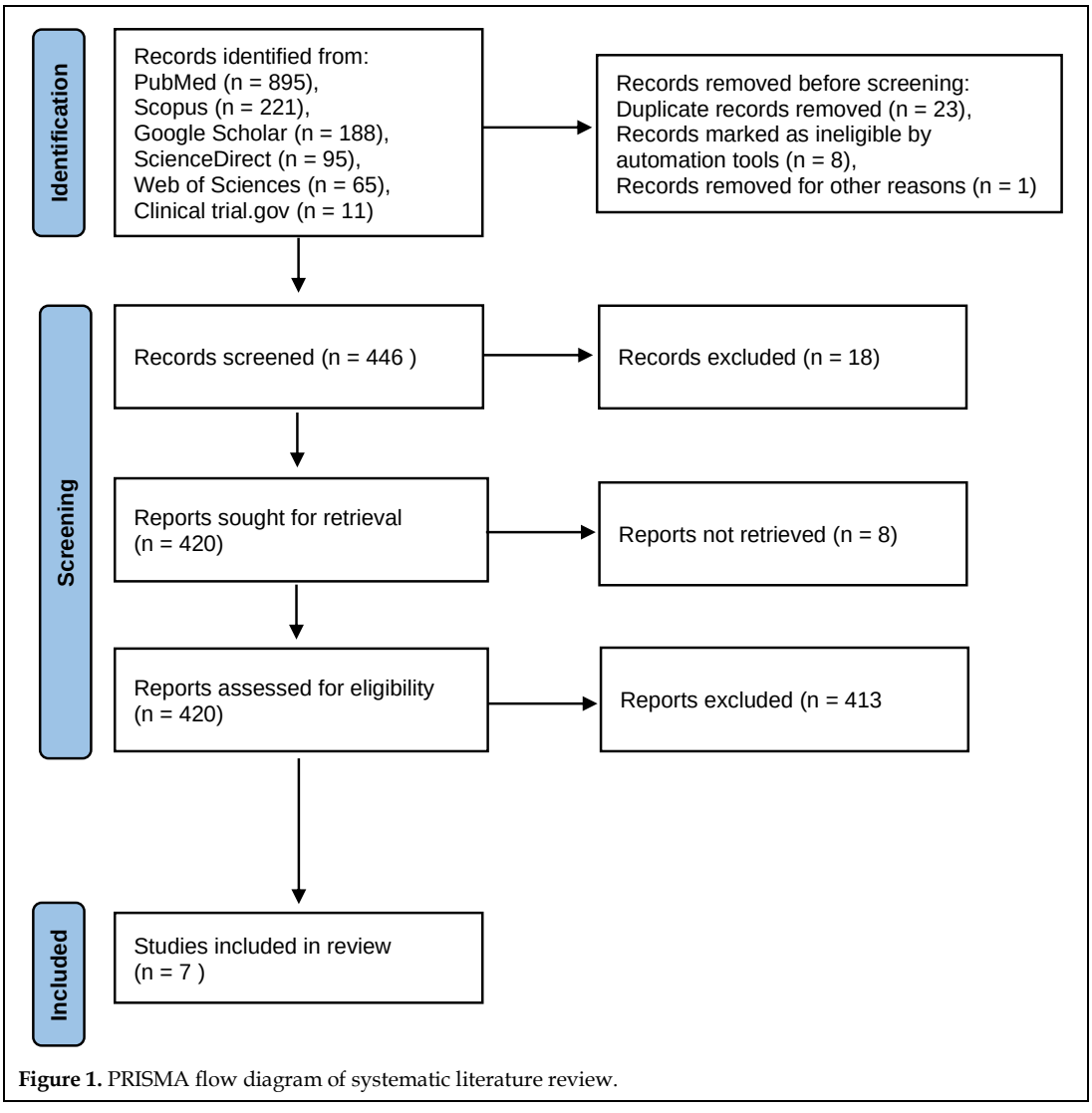

Figure 1. PRISMA flow diagram of systematic literature review.

Eligibility

One of the most important steps in systematic reviews is the eligibility assessment, which aims to ensure that the articles included are within the scope of the study. This was carried out manually by the researchers through reading the articles. Studies were considered eligible for our review if they were written in English, conducted as a randomized controlled trial or as an observational study, and fit within the scope of our aims. Those that used antazoline without a defined protocol, as well as those that were reviews or case studies, were excluded. Study selection and exclusion were conducted separately by two researchers to eliminate the risk of bias.

Quality appraisal

The quality of the selected manuscripts was assessed independently by all the authors of this study using the Scottish Intercollegiate Guidelines Network (SIGN), a tool used for quality assessments and detecting the potential risk of bias in a study. SIGN provides a checklist for each study type (e.g., cohort, RCTs, case-control, systematic reviews, and meta-analysis, among others) and assigns a grade to each article based on the number of criteria met or not met (Baker et al., 2010). Eventually, the appraised articles are categorized as high, acceptable, and low quality. None of the manuscripts included in this study were in the low category (Table 1).

Data extraction and analysis

The selected manuscripts were analyzed for qualitative synthesis, and the following data were extracted: first authors' last names, year and location of the study, study design, sample size, dose of administered antazoline, type of AF treated, and treatment outcome.

RESULTS AND DISCUSSION

To the best of our knowledge, this is the first systematic review of antazoline. Table 2 displays the selected manuscripts in chronological order.

Pharmacokinetics

There is limited data on the pharmacokinetic profile of antazoline. When administered intravenously, antazoline has a rapid onset of action within 5 min. Plasma concentrations are highest after IV administration and rapidly decline, with antiarrhythmic action lasting for approximately 1 h (Palimonka et al., 2020). The metabolism of antazoline has recently been studied in plasma and *in vitro* cultures of human hepatocytes. At least 15 potential metabolites were identified, with CYP2D6 being the main CYP isoform involved in antazoline metabolism. Further studies are required to assess the activity and safety profile of these metabolites. Hence, provide a more in-depth understanding of antazoline's clinical applications (Giebułtowicz et al., 2020). The elimination half-life following a single intravenous dose of antazoline (100 mg) was approximately 2.3 h, with a mean residence time of 3.45 h (Giebułtowicz et al., 2016). According to Dreifus et al. (1963), IV bolus doses of antazoline can be safely administered every 2-3 h. In animal studies on rats, antazoline was primarily eliminated through renal excretion (Wang et al., 2013).

Mechanism of action of antazoline (pharmacodynamic properties)

Antazoline exerts its antihistaminic action by selectively inhibiting the H1 receptor, thereby relieving the symptoms of allergic conjunctivitis (Simon and Simons, 2008). The mechanism of the antiarrhythmic action of antazoline is still inconclusive, but it may be mediated through altering membrane permeability to sodium and potassium currents(Bińkowski et al., 2018). Antazoline was found to prolong the duration of the action potential, prolong phase 0 (mediated by fast inward Na^{2+} channels), and reduce the resting potential of phase 4 (early diastolic depolarization mediated by HCN channels) (Maciag et al., 2017). Antazoline has been shown to reduce cardiac excitation, prolong atrial refraction time, and improve atrioventricular conduction, allowing the ventricles to keep up with the fast atrial rhythm (Frommeyer et al., 2017).

Hemodynamic and electrocardiographic parameters

Antazoline has been shown to induce pronounced changes in hemodynamic and electrocardiographic (ECG) parameters. A study by Piotrowski et al. (2017) investigated these effects by administering antazoline intravenously (three consecutive doses of 100 mg each) to ten healthy volunteers and measuring hemodynamic and ECG parameters using impedance cardiography. Antazoline significantly increased the P wave duration, QRS complex, QT and QTcF intervals. These results indicated a drug-induced prolongation of conduction (P wave and QRS) and repolarization (QT/QTcF). Furthermore, antazoline reduced stroke volume from baseline values (94.9 ± 21.8 vs 82.4 ± 19.6 mL, $p<0.05$). This suggests that antazoline is associated with a negative ionotropic effect, limiting its use in AF patients with organic heart disease such as heart failure. The study also indicated a strong correlation between changes in hemodynamic and ECG parameters and plasma level of antazoline.

Table 1. Quality appraisal of the selected studies using the Scottish Intercollegiate Guidelines Network (SIGN) checklist.

Author (Year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Remark
Piotrowski et al. (2014)	Yes	Yes	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	Yes	N/A	Yes	Yes	+	Yes	Yes	Acceptable
Balsam et al. (2015)	Yes	Yes	N/A	Yes	N/A	N/A	Yes	Yes	Cannot say	Yes	N/A	N/A	Yes	Yes	+	Yes	Yes	Acceptable
Farkowski et al. (2016)	Yes	Yes	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	Yes	N/A	Yes	Yes	+	Yes	Yes	Acceptable
Maciage et al. (2017)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	0%	Yes	N/A	++	Yes	Yes	-	-	-	-	High
Wybraniec et al. (2018)	Yes	Yes	N/A	Yes	N/A	N/A	Yes	Yes	Cannot say	Yes	N/A	N/A	Yes	Yes	+	Yes	Yes	Acceptable
Farkowski et al. (2018)	Yes	Cannot say	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	N/A	N/A	Cannot say	Yes	+	Yes	Yes	Acceptable
Farkowski et al. (2019)	Yes	N/A	N/A	Yes	N/A	Cannot say	Yes	N/A	Yes	Yes	Yes	Cannot say	Yes	Yes	+	Yes	Yes	Acceptable

SIGN checklist for cohort studies:

Q1. The study addresses an appropriate and clearly focused question.

Q2. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

Q3. The study indicates how many of the people asked to take part did so, in each of the groups being studied.

Q4. The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.

Q5. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.

Q6. Comparison is made between full participants and those lost to follow up, by exposure status.

Q7. The outcomes are clearly defined.

Q8. The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.

Q9. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.

Q10. The method of assessment of exposure is reliable.

Q11. Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.

Q12. Exposure level or prognostic factor is assessed more than once.

Q13. The main potential confounders are identified and taken into account in the design and analysis.

Q14. Have confidence intervals been provided?

Q15. How well was the study done to minimize the risk of bias or confounding?

Q16. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?

Q17. Are the results of this study directly applicable to the patient group targeted in this guideline?

*SIGN checklist for controlled trials:
Q1. The study addresses an appropriate and clearly focused question.
Q2. The assignment of subjects to treatment groups is randomized.
Q3. An adequate concealment method is used.
Q4. The design keeps subjects and investigators 'blind' about treatment allocation.
Q5. The treatment and control groups are similar at the start of the trial.
Q6. The only difference between groups is the treatment under investigation.
Q7. All relevant outcomes are measured in a standard, valid and reliable way.
Q8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?
Q9. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).
Q10. Where the study is carried out at more than one site, results are comparable for all sites.
Q11. How well was the study done to minimize bias?
Q12. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?
Q13. Are the results of this study directly applicable to the patient group targeted by this guideline?

Possible answers to SIGN checklist questions: Yes; No; Cannot say; Not applicable (N/A).
Cannot say: Insufficient details to allow an assessment to be made.

++: High quality
+: Acceptable

Table 2. Characteristics of the included studies.

Authors, year, location	Sample size (number of patients)	Study design	Dose and route of administration	Arrhythmia that responded to antazoline	Comments
Piotrowski et al., (2014), Poland	290	Retrospective analysis of database	IV: 100 mg injected over 2-3 min, repeated at intervals of 1 min, maximum dose not exceeding 400 mg	AF in WPW syndrome patients undergoing ablation	Mean time for cardioversion 425 ± 365 s
Balsam et al., (2015), Poland	141	Retrospective study	IV: 30–50 mg/min, maximum cumulative dose 500 mg	AF during PVI	Antazoline treatment was terminated in 7 patients due to side effects.
Farkowski et al. (2016), Poland	432	Retrospective study	IV: 50-100 mg at intervals of 3-5 min, maximum dose 350 mg	Recent onset AF Recent onset AF in patients with stable CAD.	Antazoline- based cardioversion was more effective than propafenone- based strategy.
Maciag et al., (2017), Poland	74 (Antazoline group: 36 Control group: 38)	Randomized, double-blind, placebo-controlled trial	IV: 50 mg diluted to 10 cm^3 at intervals of 5 min, maximum dose 250 mg-50 cm^3 Control group: 0.9% saline in boluses of 10 cm^3 every 5 min, maximum volume of 50 cm^3	Paroxysmal AF	Median time to conversion 16min. Successful conversion: 72.2% patients treated with antazoline 10.5% in the control group
Farkowski et al. (2018), Poland	334 (CAD group: 138. Control group: 196)	Retrospective study	IV: CAD group 152 ± 72 mg. Control group: 164 ± 69 mg	Short-duration AF with stable CAD.	Antazoline was safe and effective in patients with stable CAD (even those with a history of MI)
Wybraniec et al. (2018), Poland	109 antazoline alone 71 antazoline + other AADs	Retrospective observational	IV: either undiluted 100-200 mg or diluted with 100 mL of 0.9% NaCl, infused over 5-15 min	AF	Higher rate of cardioversion in patients treated with antazoline alone compared to those treated with combination therapy
Farkowski et al. (2019), Poland	14	Prospective study	IV: 250 mg. Maximum cumulative dose of 300 mg	Recent-onset paroxysmal AF Recent-onset persistent AF	Antazoline was effective in all patients. Mean time to conversion 8.4 ± 6.2 min

AF: atrial fibrillation; WPW: Wolff-Parkinson-White; PVI: pulmonary vein isolation; CAD: coronary artery disease; MI: myocardial infarction; AADs: antiarrhythmic drugs.

Binkowski et al. (2018) demonstrated that, unlike other antiarrhythmic drugs, antazoline had no negative effect on atrioventricular and sinus node conduction. The study examined the effect of increasing antazoline doses (100, 200, and 300 mg IV bolus) on the electrophysiological parameters of the atrial conduction system of 15 patients undergoing invasive electrophysiological study (EPS) and ablation of supraventricular arrhythmia. Antazoline dose increases were not associated with changes in the sinus node recovery period (SNRT), atrioventricular node refractory time (AVN-ERP), or Wenckebach point.

Efficacy of antazoline

The antiarrhythmic properties of antazoline were observed in animals in the middle of the last century (Dutta, 1948; Angelakos, 1959). Antazoline showed higher efficacy than quinidine in inhibiting spontaneous and surgically induced ventricular fibrillation in hypothermic dogs (Angelakos and Hegnauer, 1959). Frommeyer et al. (2017) tested the ability of antazoline to suppress AF in isolated rabbit hearts. The clinical efficacy of antazoline in the treatment of patients with paroxysmal atrial fibrillation has been evaluated in one randomized controlled trial and several observational and comparative studies. A single-center, randomized, double-blind, placebo-controlled, superiority clinical trial involving 74 subjects (36 of whom received antazoline) revealed a successful conversion of AF to sinus rhythm in 26 subjects treated with antazoline and four in the control group: RR 6.86 (95% CI: 2.66–17.72, $p<0.0001$) (Maciag et al., 2017). The secondary endpoint in this trial was the time to conversion, which was 16.0 min in the antazoline group and 72.5 min in the control group ($p = 0.0246$). Similar findings were presented by a retrospective case-control study, in which antazoline was given to 138 patients with a stable coronary artery disease (CAD) (Farkowski et al., 2018). Treatment of patients with antazoline showed successful cardioversion of AF in 82.6% of patients. Back in the seventies, Kehler and Gehring (1970) treated 20 AF patients using antazoline. Farkowski et al. (2019) evaluated the effectiveness of antazoline in cardioversion of atrial fibrillation induced during pulmonary vein isolation by assessing atrio-venous conduction before and after the IV administration of antazoline. Antazoline was effective in all cases ($n = 5$) and with no effect on Wenckebach point and atrial conduction times. The same research group analyzed 1984 medical records to see the effectiveness of antazoline in treating patients with AF (Wybraniec et al., 2018). Their findings revealed that antazoline had the highest success rate in cardioversion of atrial fibrillation (85.3%), followed by propafenone (78.6%) and amiodarone (66.7%). Antazoline alone resulted in a higher rate of cardioversion than amiodarone and/or propafenone combined (68.1%; relative risk, 1.25; 95% confidence interval, 1.12–1.40, $p = 0.0001$). In addition, antazoline was compared with propafenone by the same research group (Farkowski et al., 2016). Of the 432 cases of cardioversion analyzed, treatment of patients with antazoline was more effective as the cardioversion rate was 71.6% *versus* 55.1% for those who received propafenone. Another retrospective observational study was carried out in several medical centers to assess the effectiveness of antazoline in treating patients with AF (Wybraniec et al., 2020). Of the 1300 patients included in the study, 593 were given antazoline, 287 were given amiodarone, 150 received propafenone, 6 were given sotalol, and 264 received overlapping antiarrhythmic treatment. The rhythm conversion rates of antazoline, propafenone, and amiodarone were 78.2, 72.7, and 66.9%, respectively.

Safety profile

Overall, antazoline was generally well tolerated by patients recruited for the clinical trial discussed in the previous section (Maciag et al., 2017). Due to its poor selectivity, antazoline may cause hot flushes (19.4%), drowsiness (8.3%), headache (5.6%), nausea (5.6%), and less frequently, a bitter taste or anxiety (2.8%). Additionally, hypotension is expected when antazoline is administered rapidly. The majority of these adverse effects had minor clinical significance. The incidence of hospitalization due to antazoline adverse effects ranged from 1.4% to 4.1% in previous observational studies (Farkowski et al., 2016; 2018; Wybraniec et al., 2018).

When administered intravenously, antazoline showed no serious adverse effects (Farkowski et al., 2019). This drug, when given at high doses may affect the cardiac function (decrease the cardiac output) (Srzednicki et al., 1990), induce neurologic adverse effects such as hallucination and tremors of the hand, cause widening of the QRS complex and decreased myocardial contractility, and lead to depression (Reynolds Jr et al., 1964; Maciag et al., 2017). Therefore, antazoline should not be given to patients with heart failure, particularly those with advanced third-degree heart block. Some authors identified a connection between potassium concentration and antazoline efficacy. Leön-Sotomayor et al. (1963) proposed that to maximize antazoline efficacy, potassium levels should be corrected if there are any deficits prior to antazoline administration.

Dosage and administration

In the past, antazoline was given orally with a starting dose of 100 mg three times daily and this dose was increased in case of low response (Kline et al., 1962; Dreifus et al., 1963; Leön-Sotomayor, 1963). Nonetheless, due to its adverse effects, the antazoline dose was minimized according to recent studies. For the purpose of cardioversion of AF, antazoline was given intravenously in divided doses of 50 mg every 3-5 min up to a cumulative dose of 250-300 mg (Farkowski et al., 2016; Maciag et al., 2017). Beyond 300 mg the incremental effectiveness of antazoline is marginal, but the risk of adverse effects increases significantly (Farkowski et al., 2019).

Limitations

Our study is limited by the presence of a comparable review by Palimonka et al. (2020), which collected studies on the use of antazoline for a variety of supraventricular arrhythmias. Unlike their review, we focused our literature search on studies that used intravenous antazoline for the purpose of cardioversion of recent-onset AF. We found that antazoline-based cardioversion was both safer and more effective than amiodarone and propafenone based-cardioversion. This, however, was based on a single comparative effectiveness study. Additional RCTs comparing antazoline with other antiarrhythmic agents in the emergency department are needed.

CONCLUSION

Taken together, while antazoline has emerged as a promising antiarrhythmic drug for the rapid cardioversion of recent-onset atrial fibrillation and restoration of sinus rhythm, further randomized controlled trials are required to confirm its safety and efficacy before it can be approved for global marketing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Aldulaymi R	Al Meslamani AZ
Concepts or ideas	x	x
Design	x	x
Definition of intellectual content	x	
Literature search	x	x
Experimental studies	x	x
Data acquisition	x	x
Data analysis	x	x
Statistical analysis	x	x
Manuscript preparation	x	x
Manuscript editing	x	x
Manuscript review	x	x

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