EDITORIAL

Antazoline: the Lazarus of antiarrhythmic drugs?

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When patients report to the emergency department (ED) with acute-onset, uncomplicated atrial fibrillation (AF), cardioversion presents an option for rapid restoration of sinus rhythm and relief of symptoms. There is an ongoing debate over cardioversion versus watchful waiting, as spontaneous reversion to sinus rhythm occurs in up to 70% of patients.[1] Individualized care should allow for either possibility after an informed discussion between the physician and the patient regarding the benefits, risks, and preferences, tailored to their specific circumstances.

When pharmacological—over electrical—cardioversion is selected, a variety of options are available, such as flecainide, propafenone, sotalol, amiodarone, dofetilide, ibutilide, and vernakalant. Many readers may be unaware that antazoline can also be utilized for this purpose. New evidence is presented in the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), and in this editorial we will explore the existing evidence base in the context of these new findings.

Antazoline is a first-generation antihistamine, exerting action via antagonism of the H1 receptor, and is commonly used in eye drops to treat allergic seasonal symptoms. As far back as 1946, it was recognized that antihistamines could exert a quinidine-like antiarrhythmic effect.[2] In the 1960s, a small trial showed that antazoline could suppress ectopy and ventricular arrhythmias but, interestingly, found no benefit in cardioversion or prevention of AF or atrial flutter.[3]

Antazoline as an antiarrhythmic was seemingly forgotten in the literature after the 1960s, though it may have continued to be used in some regions of Europe. Its revival began in 2012 (Supplementary material, *Figure S1*).

In the current edition of *Pol Arch Intern Med*, Wybraniec et al[4] present the results of a propensity score matched (PSM) registry analysis utilizing antazoline for pharmacological cardioversion of AF. The authors retrospectively analyzed 1365 ED attendees with recent-onset AF in a multicenter registry, all of whom underwent attempted pharmacological cardioversion. The choice of drug was at the discretion of the physician and consisted of amiodarone, propafenone, antazoline, or a combination thereof. Success was defined as restoration of sinus rhythm within 12 hours. Of note, the patients who underwent electrical cardioversion following drug therapy, but before 12 hours, were excluded.

The analysis was performed for the overall cohort and for PSM antazoline vs non-antazoline groups. Successful cardioversion with any drug was achieved in 70.7% of patients, with the safety end point being met in 4.8%, mostly due to bradycardia (4.1%). In the non-PSM cohorts, antazoline was successful in 78.3% of cases and outperformed amiodarone (66.9%; P <0.001) and a composite group of combination therapies (59.2%; P <0.001) but was not statistically superior to propafenone (72.7%; P = 0.14). The safety end point was more frequently met in the antazoline group (5.2%) than in the amiodarone group (2.1%; P = 0.03), and occurred at a similar rate as in the propafenone cohort (7.3%; P = 0.3). Again, bradycardia was the most frequent adverse effect. Similar findings were seen following PSM.

The authors should be congratulated for demonstrating the safety and efficacy of a medication which is relatively unknown in most countries. However, a few points are worth considering.

Firstly, registry data are invaluable for demonstrating real-world practice, but are subject to uncontrollable bias, even despite PSM. For example, physician discretion to choose antiarrhythmics may mean that those given antazoline were more suited to this drug in some unmeasured way. PSM can correct for multiple measured variables but only randomization can control for unmeasured confounding. Hence, whilst this study provides

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Received: May 16, 2022.
Accepted: May 17, 2022.
Published online: June 29, 2022.
Pol Arch Intern Med. 2022; 132 (6): 16264
doi:10.20452/pamw.16264

TABLE 1 Summary of the current clinical evidence base for antazoline in cardioversion of atrial fibrillation

Study	Type	N	Setting	Findings	Side effects
Piotrowski et al,[10] 2014	Prospective observational	12	Accessory pathway ablation	Antazoline successfully terminated AF, which developed during AP ablation, in 100% of cases.	None
Balsam et al,[11] 2015	Prospective observational	141	Pulmonary vein isolation	Antazoline terminated AF during PVI procedures with an efficacy of 83.6% (paroxysmal AF)/31.1% (persistent AF).	Nausea (2.1%), RBBB (1.4%), nonsustained VT (0.7%), hypotension (0.7%). All adverse effects resolved within 15 minutes of infusion cessation.
Farkowski et al,[12] 2016	Retrospective case-control	432	Emergency department	Antazoline outperformed propafenone for acute cardioversion of AF (71.6% vs 55.1%; $P = 0.002$).	Hypotension (1.8%), bradycardia (9.6%); no statistical difference as compared with propafenone. Other mild side effects not described in detail.
Maciąg et al[5] (AnPAF), 2017	Single-center randomized controlled trial	74	Emergency department	Antazoline outperformed placebo for acute cardioversion of AF (72.2% vs 10.5%; $P < 0.0001$).	Hypotension (2.8%), tachycardia (5.6%), hot flush (19.4%), drowsiness (8.3%), headache (5.6%), nausea (5.6%), heart failure (2.8%), bradycardia (5.6%).
Wybraniec et al[13] (CANT), 2018	Retrospective observational	450	Emergency department	Antazoline was successful in 85.3% of cases, outperforming amiodarone (66.7%; $P < 0.001$) and performing similarly to propafenone (78.6%; $P = 0.317$).	No adverse events reported in the antazoline group.
Farkowski et al,[14] 2018	Retrospective observational	334	Emergency department	Antazoline was more effective in patients with CAD than those without (82.6% vs 63.8%; $P = 0.0002$).	Chest discomfort (1 patient), bradycardia with sinus node dysfunction (1 patient). No interaction with prior MI was noted.
Farkowski et al,[15] 2022	Retrospective observational	334	Emergency department	Antazoline was similarly effective in patients over or under 75 years (78.2% vs 68.3%; $P = 0.06$).	Hypotension (6 patients), bradycardia (32 patients); effects were similar between arms. Hospitalization for adverse events was numerically higher in the <75 years arm (9 vs 1; $P = 0.17$).
Wybraniec et al,[4] 2022	Retrospective observational	1365	Emergency department	Antazoline was successful in 78.3% of cases, outperforming amiodarone (66.9%; $P < 0.001$) and performing similarly to propafenone (72.7%, $P = 0.14$).	Bradycardia (4.8%), hypotension (0.8%). Composite safety end point was higher for antazoline vs amiodarone but similar to propafenone.

Abbreviations: AF, atrial fibrillation; AP, accessory pathway; CAD, coronary artery disease; MI, myocardial infarction; N, number of patients; PVI, pulmonary vein isolation; RBBB, right bundle branch block; VT, ventricular tachycardia

valuable information, it cannot supplant randomized controlled trial (RCT) data.

Secondly, the decision to exclude the patients who underwent electrical cardioversion within 12 hours of the drug exposure is questionable. The authors gave a sound reason, namely, to avoid underestimation of efficacy of the drugs with a longer onset of action, such as amiodarone. The effect of doing so, however, leads to exclusion of patients who may have undergone electrical cardioversion emergently; for example, due to hemodynamic instability or conversion to 1:1 atrial flutter. For this reason, conclusions about the safety of antazoline must be interpreted with caution.

Thirdly, 24% of the patients received more than 1 antiarrhythmic drug, and 14 patients (1%) received 3 drugs. The wisdom of additive antiarrhythmics must be questioned: if a single drug has failed, adding 1, or especially 2, further antiarrhythmics increases the risk of side effects and proarrhythmia substantially. In the setting of failed cardioversion with a single agent, the wisest course would be a change of strategy, either to electrical cardioversion or rate control.

There are few studies of antazoline, and all originate from Poland, which limits the generalizability to a wider global population.

The only RCT of antazoline for AF was the AnPAF study,[5] published in 2017. This was a single-center study of 74 patients, which assessed the efficacy and safety of antazoline vs placebo for cardioversion of recent-onset AF. The primary efficacy end point (cardioversion to sinus rhythm within approximately 2 hours) was met in 72.2% of the antazoline arm vs 10.5% of the placebo arm ($P < 0.0001$), with a median time-to-cardioversion of 16 minutes. Most adverse events were mild and transient, although 1 patient required admission due to dyspnea and congestion.

The remainder of the evidence base consists of observational studies (TABLE 1).

The quinidine-like action of antazoline suggests a Vaughan–Williams class I effect. A study on healthy volunteers demonstrated hemodynamic effects similar to those of other class I agents, with negative inotropy and prolongation

of the P-wave, QRS, and corrected QT interval.[6] In invasive electrophysiological studies, antazoline caused significant interatrial conduction delay and QT prolongation without significantly affecting the AV-nodal conduction,[7] again similarly to other class I drugs.

These findings may suggest a risk if antazoline is used in individuals with structural heart disease, heart failure, or genetic QT pathology—although, interestingly, animal models demonstrated potential benefit of antazoline in long and short QT syndromes.[8] There is also a potential risk of conversion to 1:1 atrial flutter, as is seen with other class I drugs, such as flecainide.

Despite these potential risks, the studies described above did not show significant safety concerns.

Currently, the European Society of Cardiology guidelines recommend vernakalant, flecainide, or propafenone as first-line cardioversion agents.[9] Antazoline does not feature in the guidelines.

Proarrhythmia is a limiting factor for many antiarrhythmics and there is a need for effective and safe antiarrhythmics for acute cardioversion of AF. Whether or not antazoline could fill this gap remains to be proven. The current evidence base, including the present study, is limited to mostly observational studies and a single RCT, all from Polish cohorts (**TABLE 1**). These studies do show potential benefits, with encouraging success rates and cardioversion frequently achieved in less than half an hour. However, further research is warranted in more diverse populations before this drug can be endorsed strongly.

In conclusion, antazoline—a "lost-and-found" antiarrhythmic—shows promise for acute conversion of new-onset, uncomplicated AF. Successful cardioversion rates appear encouraging, and adverse events, mainly bradycardia, are relatively infrequent. However, the current evidence base is limited to mostly observational studies from a single country and larger-scale RCTs are required.

SUPPLEMENTARY MATERIAL

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

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST DG: institutional research grants from Biosense Webster, Boston Scientific and Medtronic and speaker fees from Boston Scientific; GYHL: consultant and speaker for BMS / Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. PC declares no conflict of interst.

HOW TO CITE Calvert P, Gupta D, Lip GYH. Antazoline: the Lazarus of antiarrhythmic drugs? Pol Arch Intern Med. 2022; 132: 16264. doi:10.20452/pamw.16264

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