EDITORIAL

Antazoline for pharmacologic cardioversion of atrial fibrillation: teaching an old drug new tricks

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Atrial fibrillation (AF), the most common arrhythmia in adults, is associated with significant morbidity, health care utilization, and cost burden.[1] As such, strategies that safely, effectively, and efficiently treat patients with AF presenting to a hospital are of great appeal.

In hemodynamically stable patients presenting within 48 hours of AF onset, early cardioversion (electric or pharmacologic) is a recommended approach, following consideration of thromboembolic risk. In this setting, commonly administered antiarrhythmic drugs (AADs) include flecainide, propafenone, amiodarone, ibutilide, and vernakalant. Due to the varying efficacy, safety, rapidity of onset, clinical availability, cost, and contraindication profile of these AADs,[2] the quest continues to discover novel drugs—or repurpose old ones—with more favorable profiles. This issue of *Polish Archives of Internal Medicine* presents pertinent new data in this arena, which we consider in this editorial.

Antazoline, a first-generation histamine H1 receptor antagonist, is most widely known for its use as an eye drop preparation for the treatment of allergic rhinitis. The antiarrhythmic properties of antazoline have been recognized for over half a century, although attracting little study.[3,4] Over the last decade, intravenous antazoline has emerged as a repurposed AAD for cardioversion of recent-onset AF, with purported benefits in terms of improved efficacy and safety and lower expense.[5] For example, the cost of antazoline is approximately 1.5 EUR per dose,[6] as compared with over 300 EUR for vernakalant.[7]

Although several studies have examined the use of antazoline in the setting of AF, a majority of them are limited by their observational nature.[5,8] The largest of these, a retrospective registry of over 1300 patients in Poland, reported favorable efficacy over amiodarone (78.3% vs 66.9% for conversion to sinus rhythm; P <0.001) and similar efficacy to propafenone (78.3% vs 72.7%; P = 0.14).[9] These results persisted following propensity-score matching.[9] While encouraging, such analyses are at an inherent risk of bias due to a failure to account for unmeasured confounders.[10]

To date, the only randomized controlled trial (RCT) evaluating antazoline as an AAD in AF is the AnPAF study,[11] which assessed the efficacy and safety of antazoline vs placebo in 74 patients. In this study, successful cardioversion within a 2-hour observation period occurred in 72.2% of the patients treated with antazoline and in 10.5% of the patients treated with saline control (P <0.001), with a median time-to--conversion of 16 minutes. One patient (out of 36) receiving antazoline experienced a serious adverse event (congestion responsive to diuretic therapy), while 7 patients (19.4%) experienced temporary hot flushing. Clearly, prior to its incorporation into international AF guidelines, further well-designed and adequately powered RCTs comparing antazoline to guideline-recommended AADs are necessary.

In this issue of the journal, Karwowski et al[6] present the findings of a single-center, double--blind RCT comparing intravenous antazoline to propafenone for pharmacologic cardioversion (PCV) of recent-onset paroxysmal AF. Important exclusion criteria comprised the presence of ischemic heart disease and heart failure. Following 1:1 randomization, the groups were well balanced for baseline characteristics.

The primary efficacy end point of cardioversion within a 3-hour observation period occurred in 63% of the patients treated with antazoline and in 52.1% of those treated with propafenone (P = 0.39). Notably, time-to-conversion

was shorter in the antazoline group (median, 10 vs 30 min; $P = 0.03$). From a safety perspective, the rate of serious adverse events was similar—although relatively high—in both groups (10.9% vs 10.4%, respectively, for antazoline and propafenone): in the antazoline group, 3 patients experienced pauses and bradycardia not requiring intervention, 1 developed hypotonia and confusion responding to intravenous fluids, and 1 converted to atrial flutter with 1:1 conduction with a ventricular rate of 240 bpm; in the propafenone group, 3 patients experienced pauses and bradycardia not requiring intervention, 1 developed a third-degree heart block requiring pacemaker implantation, and 1 developed congestion requiring hospital admission. The frequency of minor adverse events was similar between the groups, except for transient hot flushes, which occurred more often in the patients receiving antazoline (34.8% vs 6.2%; $P = 0.001$).

The AnProAF investigators[6] should be congratulated for their efforts in undertaking the first RCT comparing antazoline to a guideline--recommended AAD, thereby providing much needed comparative data in this evidence-free zone. In particular, we commend the authors for ensuring that both participants and health care professionals administering the study drugs were blinded to the treatment allocation, reducing the risk of bias. Importantly, as compared with propafenone, antazoline lead to significantly faster cardioversion to sinus rhythm, which the authors cite as a potential advantage for health care systems. Nonetheless, we must acknowledge several limitations of the study.

First, although reported as a superiority trial, the study is underpowered for such a design, with only 94 participants enrolled. Indeed, using a conventional superiority design, a sample size of 638 participants would have been required for an α of 5%, affording 80% power to detect a difference between successful PCV rates of 63% and 52.1% with antazoline and propafenone, respectively. In reality, if efficacy of antazoline is perceived to be similar to that of propafenone, as suggested by the authors, a noninferiority design with a predefined noninferiority margin may have been preferred, and should be considered by future investigators comparing antazoline to the established AADs.

Second, cardioversion rates were only reported up to 3 hours following the drug administration in AnProAF.[6] Although 3 hours is a clinically useful duration for predicting reversion within an emergency department, it is acknowledged that many patients with paroxysmal AF spontaneously cardiovert within 1 to 2 days, with otherwise similar clinical outcomes to those of individuals receiving PCV. Indeed, in the RACE 7 ACWAS study,[12] 69% of patients randomized to a watch-and-wait approach cardioverted within 48 hours. Failure to extend the monitoring period beyond 3 hours in AnProAF, and a lack of information on subsequent treatment in those failing to cardiovert within this time period, make extrapolation of the findings beyond the initial treatment in an emergency department challenging. This is important given the increasing use of early rhythm control as a strategy to improve clinical outcomes.[13]

Third, the single-center design and a lack of comparison to other commonly administered AADs (such as flecainide, ibutilide, and amiodarone) limit the external validity and interpretation of the study. Further multicenter—and ideally multiarmed—RCTs comparing antazoline to the established treatment options should be undertaken to determine the comparative effectiveness of each.

Fourth, we must not ignore the increasing evidence showing the importance of the holistic or integrated care approach to AF management, which has been associated with improved clinical outcomes[14] and recommended in guidelines.[15]

But more generally, and as is often the case in medicine, we should be reminded of the old adage, *If it ain't broken, don't fix it*. In order to gain traction among the wider medical community, antazoline must position itself as not only equal to established therapies, but ideally as advantageous in 1 or more ways. While the reported time--to-cardioversion with antazoline in AnProAF is statistically faster, this modest difference of 20 minutes may not be of clinical significance, as patients frequently require further observation or investigation following cardioversion, negating this advantage. Furthermore, considering the similar safety and efficacy profiles of antazoline an propafenone reported in AnProAF, future RCTs should seek to carefully document other important metrics, which may demonstrate advantages of one drug over another; in particular, cost-effectiveness and health care–associated efficiency modelling, as well as patient-reported outcomes. Only if such an advantage is identified, is antazoline likely to find widespread use.

ARTICLE INFORMATION

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