Ranolazine versus amiodarone for prevention of postoperative atrial fibrillation

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Evaluation of: Miles RH, Passman R, Murdock DK. Comparison of effectiveness and safety of ranolazine versus amiodarone for preventing atrial fibrillation after coronary artery bypass grafting. *Am. J. Cardiol.* 108(5), 673–676 (2011). Postoperative atrial fibrillation (AF) is a major complication of cardiothoracic surgery, leading to significant consequences, including a higher rate of stroke, longer hospital stays and increased costs. Amiodarone is among the most widely used agents for prevention of postoperative AF. Ranolazine, a US FDA-approved antianginal agent, has been shown to effectively, safely prevent and terminate nonpostoperative AF in both experimental and clinical studies. In a recent publication, Miles and colleagues directly compared the efficacy and safety of amiodarone and ranolazine for prevention of postoperative AF in 393 patients. The patients were pretreated with amiodarone and ranolaizne for >1 week and 1 day, respectively, and the treatment continued for 10–14 days after surgery. Following coronary artery bypass grafting (CABG), AF occurred in 26.5% of patients taking amiodarone and in 17.5% of patients taking ranolazine (34% reduction; $p < 0.035$). No differences in adverse events between the two groups of patients were recorded. The results of this retrospective nonrandomized single-center study indicate that ranolazine may be used to effectively and safely prevent postoperative AF. These results need to be confirmed in a larger randomized study. If confirmed, ranolazine may be a good choice for preventing AF in patients undergoing CABG.

Over 750,000 cardiothoracic surgeries (i.e., coronary artery bypass graft [CABG] and heart valve) are performed annually in the USA alone. Postoperative atrial fibrillation (AF) is a major complication of cardiothoracic surgery, occurring in 10–64% of patients, commonly on the second to fourth day after surgery, and leads to significant consequences including a higher rate of stroke, longer hospital stays and increased costs [1–3]. The arrhythmia usually terminates spontaneously (in 90% patients within 6–8 weeks after surgery) [4]. Commonly used clinical treatments designed to prevent postoperative AF include administration of β-blockers, amiodarone, sotalol and ibutilide. Statins have recently been included in this list in the European Union [5]. Direct current cardioversion is often used to terminate postoperative AF in hemodynamically unstable patients.

A wide variety of factors are thought to participate in the production of postoperative AF, including: preoperative atrial conduction abnormalities, cardioplegic arrest-induced ischemic-reperfusion injury, inflammation (i.e., pericarditis), increased adrenergic tone, autonomic imbalance, acute stretch, hormonal alterations, production of free radicals, intracellular calcium loading, coronary artery stenosis and genetic predisposition [2,5]. Most of these arrhythmogenic mechanisms are transient, accounting for the transient nature of postoperative AF in most patients. Because of the participation of multiple physiological and pathophysiological factors, the mechanisms underlying postoperative AF are complex and relatively poorly understood.

Amiodarone

Amiodarone is an antiarrhythmic agent that acts via inhibition of multiple cardiac ion currents (including sodium, potassium and calcium currents) and blocks α- and β-adrenoceptors [6]. Chronic amiodarone blocks peak I_{Na} preferentially in atria versus ventricles [7]. In the clinic, acute and chronic amiodarone are widely used in the management of atrial and ventricular arrhythmias [8,9]. Amiodarone is often considered to be the best pharmacological agent currently available for the long-term maintenance of sinus rhythm in AF patients, but its long-term use causes extra-cardiac multi-organ toxicity in many patients [8]. Amiodarone is among the most widely used agent to prevent postoperative AF and the drug can reduce

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postoperative AF and reduce the duration of hospital stays and the incidence of postoperative stroke [5,10].

The antiarrhythmic efficacy of amiodarone has been related to a number of factors including APD/ERP prolongation, reduction of dispersion of repolarization, induction of PRR, prolongation of excitable gap, suppression of triggered activity and inhibition of atrial electrical and structural remodeling [8,9,11–13].

Ranolazine

Ranolazine is a US FDA-approved antianginal agent with antiarrhythmic efficacy. The ion channel block profile of ranolazine is similar to that of chronic amiodarone [14]. Ranolazine inhibits late I_{Na}, peak I_{Na}, I_{Kr} and I_{Ca}, as well as β-adrenoreceptors [14,15]. Similar to amiodarone [7], ranolazine inhibits peak I_{Na} in an atrial selective manner [15]. Ranolazine exerts antiarrhythmic effects in both ventricles and atria. In the ventricles, ranolazine can suppress arrhythmias associated with acute coronary syndrome, long QT, heart failure, ischemia, and reperfusion [16]. Ranolazine has been shown to terminate AF and prevent its induction in several experimental models [15,17,18]. This drug effectively suppresses vagally mediated AF in isolated canine atria [15] and significantly shortens vagally mediated AF in porcine hearts *in vivo* [18]. In canine isolated pulmonary vein preparations, ranolazine suppresses the common triggers of AF initiation (i.e., delayed after depolarization and late phase 3 early after depolarization activity) [17,19]. In isolated atrial guinea pig myocytes, delayed after depolarizations and early after depolarizations induced by an increase of late I_{Na} and automaticity induced by hydrogen peroxide are effectively suppressed by ranolazine [20,21].

Clinical anti-AF efficacy of ranolazine has been demonstrated in several studies. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes – Thrombolysis in Myocardial Infarction (MERLIN-TIMI) 36 trial, ranolazine treatment was associated with a significant reduction of supraventricular tachyarrhythmias ($p < 0.001$) as well as a 30% reduction in new onset AF ($p = 0.08$) [22]. Subsequently, results of a number of small exploratory clinical studies have demonstrated an anti-AF efficacy of ranolazine in termination of paroxysmal AF [23,24]. Results of one study suggest that a single dose of 2000 mg ranolazine is an effective 'pill-in-the-pocket' approach, converting 77% of AF patients to sinus rhythm with no significant adverse reactions, including patients with structural cardiac abnormalities [24]. Considering the safety of ranolazine in patients with structural heart disease [25,26] the 'pill-in-the-pocket' approach utilizing ranolazine may have a much wider applicability than previously used Class IC antiarrhythmic agents (i.e., propafenone and flecainide) [27]. Owing to a high risk of adverse effects, these agents are contraindicated in patients with structural heart disease, which occurs in a majority of AF patients. The results of the clinical studies are encouraging, but larger and multicenter clinical trials to evaluate the efficacy and safety of ranolazine in the management of patients with AF are needed.

The mechanism underlying ranolazine's antiarrhythmic actions in the ventricles is thought to be primarily via inhibition of late I_{Na}, which leads to reduction in dispersion of repolarization, decrease in intracellular calcium loading and suppression of triggered activity [16]. The antiarrhythmic mechanism underlying the effect of ranolazine to suppress AF includes several factors. The main factor entails block of peak I_{Na}, which reduces excitability, thus leading to use-dependent prolongation of ERP, due to development of PRR [15]. The net result is failure of rapid activation of the atria. The effect of ranolazine to prolong APD_{90} in atria, secondary to its action to block I_{Kr}, serves to synergize the effect of the drug to block peak I_{Na} by reducing the diastolic interval, during which the Na channel recovers from drug block. As a result of its action to block peak and late I_{Na} as well as I_{Ca}, ranolazine reduces intracellular calcium activity, thus suppressing delayed after depolarization- and early after depolarization-mediated triggers of AF [17]. The short- and long-term safety of ranolazine has been demonstrated in the clinic, even in patients with structural heart disease [25,26].

Amiodarone versus ranolazine against postoperative AF

The recent report by Miles and colleagues involved a study that directly compared the efficacy of amiodarone and ranolazine to prevent postoperative AF in 393 patients undergoing CABG (211 and 182 patients, respectively) [1]. Amiodarone treatement was usually started 7 days before the operation (400 mg/day) and was continued for 10–14 day after surgery (200 mg twice daily). Ranolazine treatment was generally started the day before surgery (1500 mg), or in very urgent cases, the day of surgery. It was then continued for 10–14 days at

1000 mg twice daily postoperatively. Following CABG, AF occurred in 26.5% patients taking amiodarone and in 17.5% patients taking ranolazine (34% reduction; $p < 0.035$). No differences in adverse events between amiodarone and ranolazine groups were recorded.

The study was not placebo-controlled and there were some differences between the amiodarone and ranolazine-treated patients, which might have contributed to the results. A confounding factor was that the average left ventricular ejection fraction (LVEF) was slightly but statistically significantly lower in the amiodarone versus ranolazine group (54.7 ± 12.7 vs 57.7 ± 9.8%, respectively; $p = 0.01$). The relationship between the prevalence of AF (non- and post-operative AF) and LVEF is very complex and poorly studied. Generally, the tendency is that AF prevalence (nonoperative) is greater in HF patients with preserved LVEF versus HF patients with reduced LVEF [28–31]. It is unclear if the differences in LVEF in the ranolazine versus amiodarone groups contributed to the incidence of postoperative AF.

Future perspective

Postoperative AF remains a major complication of cardiothoracic surgery, which needs to be addressed. Safer and more effective approaches for the prevention of postoperative AF are desirable. The results of the study by Miles *et al.* indicate that ranolazine can effectively and safely prevent the appearance of postoperative AF and anti-AF efficacy of ranolazine is better than that of amiodarone [1]. Amiodarone treatment for prevention of postoperative AF is generally recommended to commence between 1–2 week preoperatively, which may be impractical for many patients. Ranolazine, having a much shorter time needed to achieve its full effects than amiodarone, can be given 1 day before surgery or even in the day of surgery. In this respect, ranolazine seems to have an advantage over amiodarone.

'Safety first' is a prime principle of the antiarrhythmic pharmacology. Short- and long-term safety of ranolazine has been demonstrated in the clinic, even in patients with structural heart disease [25,26]. Amiodarone-induced adverse effects are commonly associated with its long- rather than short-term treatment. Since the pharmacological treatment period for prevention of postoperative AF is relatively short (2–3 weeks), relative safety of ranolazine versus amiodarone may not be very different. In conclusion, while the results of the study by Miles *et al.* are promising, larger controlled randomized studies are needed to confirm anti-AF efficacy and safety of ranolazine in patients undergoing CABG.

This demonstration of a superiority of ranolazine over amiodarone for suppression of postoperative AF begs the question of whether such superiority extends to suppression of AF in other settings, in which case clinical trials would be most welcome. Finally, in light of the very impressive anti-AF synergy observed when

Executive summary

Background

- Postoperative atrial fibrillation (AF) remains a major complication of cardiothoracic surgery leading to a higher rate of stroke, longer hospital stays and consequently higher costs. Safer and more effective approaches for prevention of postoperative AF are desirable. Amiodarone is often used for prevention of postoperative AF.

Methods

- The retrospective single-center nonrandomized study compared amiodarone versus ranolazine for the prevention of AF after coronary artery bypass grafting.

Results

- Postoperative AF occurred in 26.5% patients taking amiodarone and in 17.5% patients taking ranolazine (34% reduction; $p < 0.035$). No differences in adverse events between the two groups of patients were recorded.

Significance

- This is the first study directly comparing efficacy and safety of amiodarone and ranolazine to prevent postoperative AF and demonstrating the anti-AF superiority of ranolazine.

Future perspective

- Ranolazine may be more effective than amiodarone for prevention of postoperative AF. Larger controlled randomized trials are needed to confirm the efficacy and safety of ranolazine against amiodarone in postoperative AF. Clinical trials would also be welcome to examine whether the anti-AF superiority of ranolazine over amiodarone extends to other AF settings. Finally, it would be of interest to study whether the combination of the two drugs may be still more potent in suppressing AF postoperatively as well as in other settings.

combining amiodarone and ranolazine in experimental studies [32], it would be of great interest to test the hypothesis that the combination of the two drugs may still more potently suppress AF postoperatively as well as in other settings.

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