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Heart failure, atrial fibrillation, and landiolol – a new, ultra-short-acting beta-blocker. Review of the literature

Paulina Ratajska[1], Małgorzata Wilawer[1], Paweł Burchardt[2,3]
[1] J. Strus Hospital, Poznan
[2] Department of Hypertension, Angiology, and Internal Medicine, Poznan University of Medical Sciences, Poznań
[3] Department of Cardiology, J. Struś Hospital, Poznan

Summary

Landiolol is a new ultra-short-acting beta-blocker invented in Japan. 2022 ESC guidelines for Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death includes landiolol for use in ventricular tachyarrhythmias and electrical storm. Patients with heart failure and atrial fibrillation, regardless of left ventricular ejection fraction, are at higher risk of heart failure exacerbation, including hospitalization and death from HF exacerbation; thus, it is essential to maintain ventricular rate control. This review summarizes up-to-date knowledge of the use of landiolol in patients with heart failure and atrial fibrillation. *(Farm Współ 2023; 16: 233-238) doi: 10.53139/FW.20231633*

Keywords: landiolol, atrial fibrillation, heart failure, beta-blocker

Introduction

Landiolol is an ultra-short-acting beta-blocker with a 9-fold higher beta-adrenergic potential and 8-fold more cardioselective (B1/B2 = 255) than esmolol [1]. According to the 2022 ESC guidelines for Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, this review summarizes the current state of the art considering landiolol, its differences from other beta-blockers and clear indications for its clinical use [2].

Main text

Since landiolol was invented in Japan and approved for use in 2002, the first reports on the use of landiolol in vivo came from this country. Initially, several case reports of successful use of landiolol in patients with tachyarrhythmias were published, e.g., with atrial fibrillation (AF), tachyarrhythmia secondary to pheochromocytoma or during coronary artery bypass grafting (CABG) [3-9]. In all cases, the heart rate (HR) slowed down or the arrhythmia was suppressed, and in some cases of atrial fibrillation, a return to sinus rhythm was achieved.

The use of landiolol in heart failure was the subject of many studies. In 2012, Kobayashi et al. investigated the use of continuous infusion landiolol at a dose of 1.5 to 6 mcg/kg/min in 20 patients with NYHA class IV heart failure (HF; 1 patient had NYHA class III) as an adjunct to standard therapy of heart failure decompensation with the use of milrinone, diuretics, and vasodilators [10]. The study found that the addition of low-dose landiolol improved cardiac function while completely eliminating the occurrence of pulsus alternans in this group of patients. A dose of 1.5 mcg/kg/min was considered safe, as it significantly contributed to reducing HR without affecting blood pressure (BP) and cardiac index (CI), while significantly improving parameters such as pulmonary capillary wedge pressure (PCWP), stroke volume index (SVI), SvO2, rate pressure product (RPP), filling time/RR, E/e', and Tei index. The use of doses equal to and above three mcg/kg/min resulted in a decrease in arterial pressure and CI with a simultaneous increase in PCWP and systemic vascular resistance, which is not beneficial in patients with heart failure and may lead to further impairment of cardiac function.

A subgroup analysis of the randomized clinical trial J-Land study, including patients with NYHA class III and IV heart failure and arrhythmias in the form of AF or atrial flutter (AFL) with a systolic rate of at least 120 bpm, showed that landiolol was more helpful, regardless of the overall clinical picture, compared to

ORCID: Paulina Ratajska 0000-0003-1702-4239, Małgorzata Wilawer 0000-0002-2457-9833, Paweł Burchardt 0000-0003-0353-3470

digoxin in subjects with AF/AFL and a reduced left ventricular ejection fraction (LVEF) [11,12]. There was no difference in the incidence of adverse events between the groups; however, patients with lower systolic blood pressure (SBP) had significantly more adverse events in the digoxin group, and patients with higher SBP significantly more often in the landiolol group. In addition, 60% of the patients included in the study had end-stage renal disease (GFR =<15 ml/kg/h). Digoxin is a drug excreted by the kidneys, and in case of renal dysfunction, the digoxin dose must be reduced [13]. Landiolol metabolism is mediated by plasma esterases, and its metabolites are excreted by the kidneys. It was not shown that the use of landiolol affects kidney function; therefore, in patients with kidney disease, there is no need to modify the dose [14,15]. Thus, the authors concluded that landiolol should be preferred over digoxin as the drug of first choice for ventricular rate control in AF/AFL episodes in patients with renal failure. Moreover, a subgroup analysis from the J-Land II study suggests that renal dysfunction does not affect the efficacy and safety of landiolol in hemodynamically unstable patients with ventricular tachyarrhythmias [16].

An evaluation of the safe dose of landiolol was the subject of research involving 52 patients with NYHA class III (10) or IV (42) heart failure and an ejection fraction of 32±12% with supraventricular tachyarrhythmia. Patients received dobutamine, carperitide, or milrinone prior to beta-blocker administration. The inclusion criterion was the presence of tachyarrhythmias at or above one hour despite the use of standard treatment. Initially, patients received landiolol at a dose of 0.001 mg/kg/min under the control of HR and BP. The dose was increased, and no side effects were observed. At a mean dose of 10.8±9.4 mcg/kg/min, all patients had a significant decrease in HR (133±27 to 82±15 beats/min (P<0.01)) with no change in SBP (105±21 vs. 101±19 mmHg, P = ns) versus baseline. There was a significant improvement in LVEF from 32.3±11.9% to 39.7±6.5 (P<0.001). In cases of three patients, the supply of landiolol was discontinued due to the occurrence of asymptomatic hypotension. The authors emphasized the effectiveness of the use of landiolol for quick control of the ventricular rhythm for up to 24 hours in this group of patients and the role of landiolol as an intermediate treatment before the introduction of an oral beta-blocker, cardiac resynchronization therapy with defibrillator function (CRT-D) implantation or ablation of the pulmonary veins [17].

A retrospective analysis showed the effectiveness of landiolol treatment in patients with left ventricular dysfunction and AF/AFL (32) and refractory ventricular tachyarrhythmias (VTs) (12). In the case of atrial arrhythmias, 29 patients responded to treatment with a significant decrease in HR of almost 40% compared to baseline (152±19 to 96±17 bpm, p <0.0001) [18]. In 9 out of 29 responders, sinus rhythm returned without additional intervention. In 8 out of 10 non-responders, the use of electrical cardioversion restored sinus rhythm in 5 patients. In the group of patients with VTs (6 with electrical storm, 4 with sustained VT, and 2 with incessant nonsustained VT), the administration of landiolol suppressed arrhythmias in 7 patients. In 5 cases of hypotension, landiolol was discontinued. The authors concluded that adverse events were associated with left ventricular dysfunction and not the dose of landiolol. At the same time, it was found that a lower LVEF value and a larger left ventricular dimension in systole or diastole are possible predictors of the effectiveness and safety of landiolol treatment.

The HR optimization obtained by adding landiolol to milrinone treatment could improve heart function in patients with acute heart failure and atrial fibrillation [19]. The study involved nine patients with acute decompensated heart failure treated with vasodilators, diuretics, and milrinone who failed to achieve ventricular rate control after at least 4 hours of standard therapy. All patients had NYHA class IV heart failure and were "wet and cold" according to the Nohria-Stevenson classification. The administration of landiolol at a dose of 0.0015 mg/kg/min significantly decreased HR and PCPW while significantly increasing CI, SVI, and mixed venous blood oxygenation without affecting BP, mean right atrial pressure (RAP), and systemic vascular resistance. Using landiolol at or above 0.003 mg/kg/min reduced SVI, BP, and CI. The authors concluded that adding landiolol at a dose lower than 0.003 mg/kg/min to milrinone improved cardiac function by selectively lowering the HR.

A retrospective data of 67 patients aged 67±12 years with atrial tachyarrhythmias (AT) and acute decompensated heart failure were analyzed [20]. The average LVEF was 41±13%. Landiolol significantly reduced HR from baseline in all patients (141±17 beats/min at baseline to 99±20 beats/min at six h, P<0.001), with no significant effect on BP, including patients with severe

left heart failure defined as LVEF less than or equal to 30%. Concurrently, the decrease in HR was significantly greater in the group of patients with LVEF equal to or greater than 40% than in patients with LVEF <40% (79±16 beats/min vs. 88±14 beats/min, respectively, P=0.017). However, this difference was not significant. The median maintenance dose of landiolol was 3.0 (1.0-12.0) μg/kg/min, the median time from initiation of landiolol treatment to HR <100 bpm according to ESC recommendations amounted to 6 (0-30)h. During the administration of landiolol, sinus rhythm returned spontaneously in 15 patients and 5 with the help of electrical or pharmacological cardioversion [21].

In another study involving 101 patients with acute decompensated heart failure, reduced left ventricular ejection fraction and an episode of atrial fibrillation, landiolol was shown to be effective in controlling the ventricular rhythm leading to improvement of hemodynamic parameters and preventing the occurrence of short-term major adverse events, i.e. death from cardiac causes, the need for intravenous treatment for more than 30 days and worsening of renal function (increase in creatinine equal to or more than 0.3mg/dL in the first five days of hospitalization) [22]. Major adverse events (MAE) occurred significantly less frequently in the group of patients with mean arterial pressure above 97 mmHg and end-diastolic volume index (LVEDVI) below 84 ml/m^2. The authors concluded that patients with a relatively smaller left ventricular volume and higher pressure would benefit most from landiolol. Comparing the effectiveness of landiolol treatment among patients with acute, decompensated heart failure in NYHA class III or IV and left ventricular systolic dysfunction and (1) atrial fibrillation or (2) atrial flutter or atrial tachycardia, it was shown that despite significantly higher doses of landiolol in the AFL/AT group, HR was significantly lower in the group of patients with AF at each time of measurement (2, 12, 24h). A significant decrease in HR was achieved only in patients with AF. The number of responders to landiolol treatment was significantly higher in the AF group than in the AFL/AT group, resulting in significantly more frequent use of alternative therapy methods in the AFL/AT group. Treatment was discontinued in 9 patients due to hypotension and one patient due to bradycardia [23].

The efficacy and safety of landiolol to control ventricular rhythm in patients with AF/AFL and chronic heart failure were assessed in a retrospective study [24]. Regarding safety, 1,121 patients were included in the analysis, of which 888 were also included in the treatment efficacy analysis. 12.5% of patients (140) experienced adverse events, of which almost one-third of adverse events related to the cardiovascular system. The most common adverse event was hypotension. Bradycardia occurred in 8 patients, and ventricular arrhythmias in 6. HR reduction equal to or greater than 20% compared to baseline was achieved in 77.5% of patients. Of the 888 patients included in the efficacy analysis, 299 patients (33.7%) returned to sinus rhythm within seven days of stopping landiolol; the median time to first return to sinus rhythm was 14 hours (range 0.1-451.2 hours). The authors concluded that the supply of landiolol in this group of patients was safe and effective, and most patients achieved satisfactory ventricular rate control, regardless of the type of arrhythmia. At the same time, the relationship between the initiation of landiolol treatment, subsequent switch to oral beta-blockers, and all-cause mortality in the patients mentioned above within 180 days of initiation of landiolol treatment was analyzed [25]. Survival was shown to be significantly longer in patients who received an oral beta-blocker after treatment with landiolol (mostly bisoprolol at a mean starting dose of 1.66±1.33 mg) compared to those patients who were not prescribed an oral beta-blocker (hazard ratio 0.39 (95% confidence interval [CI] 0.28-0.55) for all-cause mortality and 0.40 (95% CI: 0.23-0.70) for death from HF), however, the inclusion of oral beta-blocker treatment was not an independent significant factor reducing the risk of death from all causes and from HF in this patient population. Within 180 days of follow-up, 146 out of 1002 patients (14.6%) died, including 39.7% due to exacerbation of HF. Comparing the use of landiolol and digoxin in patients with AF, heart failure, and reduced left ventricular ejection fraction (LVEF less than or equal to 25%), it was shown that the use of landiolol may be more effective than digoxin, and the use of landiolol should be associated with careful monitoring of haemodynamic values [26]. The use of landiolol was associated with a greater reduction in HR over 24 hours than in the digoxin group. SBP was significantly lower in the landiolol group than pre-treatment SBP, and there was no change in SBP over time in the digoxin group. At the same time, 2 cases of hypotension were reported in the group with landiolol, which resulted in discontinuation of therapy in these patients. The groups did not differ in the number of responders

within 1, 2, or 12 hours after the start of therapy, the number of patients with spontaneous return to sinus rhythm, the use of combination therapy, or the number of successful discharges.

In 2017, the assumptions of the HEARTFUL study, aiming to assess the effectiveness and safety of the use of landiolol in the treatment of tachyarrhythmias in children, including AF, AFL, and SVT in the presence of heart failure, were published [27]. The available literature is insufficient to determine the safety and effectiveness of landiolol supply in people under 18 years of age [28-30].

Discussion

Among the tachyarrhythmias in patients with heart failure, paroxysmal AF or AFL, chronic AF or AFL with rapid ventricular response, ventricular tachycardia, or supraventricular tachycardia predominate. In patients with HF, AF occurs significantly more often than in patients with other cardiological and renal diseases, i.e., DM and CKD [31]. Patients with HF and AF, regardless of left ventricular ejection fraction, are at higher risk of HF exacerbation, including hospitalization and death from HF exacerbation, than stroke, systemic thromboembolism, or major bleeding [32]. Population analysis from the TOPCAT American Trials proved that the presence of AF in patients with HFpEF is an independent predictor of cardiovascular adverse events due to the severity of HF, the increase in HF-related hospitalizations, and the increased risk of pump failure death in patients with HFpEF, particularly in advanced stage. In patients with HFpEF, atrial fibrillation predisposes to the progression of the underlying disease [33]. AF increases all-cause mortality in patients with any subtype of HF: HFpEF, HFmrEF, and HFrEF. The hazard ratio [HR, 95% CI] was 1.14 [1.06, 1.24], 1.28 [1.08, 1.51] and 1.11 [1.02, 1.21], respectively [34].

Data on the use of landiolol in non-Japanese patients are currently lacking. The first study on using this medicine in the treatment of AF/AFL showed that all Caucasian patients enrolled in the study achieved a reduction in HR [35]. The target end-point (reduction in HR≥20% or <100 bpm in 16 minutes) was achieved in 60% of patients in the group receiving continuous infusion of landiolol alone and in 40% in the group that received an extra bolus before the infusion of landiolol with no significant difference between the groups. In addition, 72% of patients achieved a significant reduction in arrhythmia-related symptoms. No health or life-threatening side effects were noted in any of the patients.

Next to hypotension, bradycardia is the most common side effect of landiolol, which resolves after dose reduction or discontinuation. An 87-year-old female patient experienced two episodes of asystole, lasting 10 and 7 seconds, during the administration of landiolol at a dose of 0.01 mg/kg/min due to an atrial fibrillation attack after intubation. When the beta-blocker infusion was stopped, the fibrillation returned, and no further episode of cardiac arrest was observed. Before the treatment, the patient was diagnosed with sinus bradycardia [36]. Cardiac arrest during the use of landiolol was also described in a 49-year-old patient with a hypermetabolic thyroid crisis and acute heart failure with reduced ejection fraction [37]. According to the SmPC, the presence of bradycardia or decompensated heart failure unrelated to arrhythmias in a patient is a contraindication to the administration of landiolol. Particular attention should be paid to the use of landiolol in patients with a history of hepatic dysfunction. The trial involved six patients with hepatic impairment and six healthy volunteers [38]. Five patients had Child-Pugh class A, and one had B class. The cause of liver injury in 5 patients was hepatitis C; in one patient, the cause was alcohol abuse. The mean plasma cholinesterase level (IU/L) in the study group was 46.5±15.4 (28-67) and in the control group it was 122.8±15.3 (107-146). There were no significant differences in the effects of landiolol between the groups or in the elimination half-life of the drug. However, it was found that in people with liver disease, the plasma concentration of landiolol increases by nearly 40%, and the volume of distribution of this drug decreases, which results in a more frequent occurrence of side effects during the use of landiolol. Thus, there is a need for continuous monitoring of parameters such as HR and BP in this group of patients. However, in the case of an 82-year-old patient with plasma cholinesterase deficiency, the administration of landiolol in a bolus of 10 mg during surgery did not result in adverse effects [39].

Conclusions

Although landiolol seems promising in patients with heart failure, more data on its effectiveness and safety are required. Among them, multicenter randomized clinical trials and large meta-analyses are lacking, especially in non-Japanese patient populations.

Conflict of interest
None

Correspondence address
💻 Paulina Ratajska
J. Strus Hospital
Szwajcarska St. 3, 61-285 Poznań
☎ (+48) 660 048 323
💻 paulrat@wp.pl

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