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Case Series Review on Landiolol in Acute Decompensated Heart Failure Secondary to Tachyarrhythmias

New Drug Applications for an Unmet Medical Need in Critically Ill Patients

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Research Letter

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Abstract

Introduction: Landiolol (Rapibloc, AOP Orphan Pharmaceuticals, Vienna, Austria) is an ultra-short-acting beta-blocker that has a half-life of 2.3–4 min. Landiolol has been used safely and successfully in patients with septic shock and atrial fibrillation and in sepsis-induced tachycardia.

Current evidence regarding the possible application of Landiolol in ADHF (Acute Decompensated Heart Failure) is very limited and confined to case reports.

Methods: We reviewed the case reports of the literature of ADHF patients treated off-label with Landiolol.

Only 11 clinical cases of Landiolol administration in ADHF were identified and reviewed in the present research.

Results and conclusions: In 11 clinically complex patients affected by ADHF, the administration of Landiolol was found to be safe and effective and favoured the restoration of a normo-frequent sinus rhythm with an improved pressure profile.

The potential therapeutic effect of Landiolol in patients with acute heart failure is under study.

New clinical uses and further clinical trials led by cardiologists and intensivists will be needed to prove the safety and efficacy of this drug.

Keywords: Landiolol; Acute Heart Failure; Sepsis-Induced Cardiac Dysfunction; Tachyarrhythmias.

Introduction:

Landiolol is a recently innovated ultra-short-acting, highly adjustable and easily titratable β1-blocker. Landiolol hydrochloride has a β1/β2 ratio of 255 and, compared to propranolol, its β1-selectivity is 74–380 times greater while it has a 33–263 times greater β1 affinity than esmolol [1,2].

Landiolol is the only beta-blocker with a specific dose recommendation for patients with cardiac dysfunction and acute atrial fibrillation (Class I recommendation according to the ESC guidelines) [3].

Like other β-blockers, Landiolol is thought to reduce the sympathetic drive and decrease the spontaneous firing of ectopic pacemakers with antiarrhythmic and anti-ischemic effects.

In contrast to esmolol, Landiolol neither blocks Na, Ca and K channels nor decreases plasma renin levels and thus exerts less effect on left ventricular function and blood pressure. In clinical trials, Landiolol reduced heart rate within 1–6 min of administration to patients with tachyarrhythmia during or after surgery, as well as in non-perioperative settings [4].

Landiolol has a shorter elimination half-life than any other beta-blocker, and it can be administered safely to patients with various tachyarrhythmias [5]. The short duration of action and titratability of Landiolol makes it ideal for use in critically ill patients, especially in elderly patients with Sepsis-induced cardiogenic shock.

From the pathophysiological standpoint, the concept of

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"inappropriate tachycardia" is emerging which worsens the outcome of septic shock patients by increasing myocardial workload and oxygen demand.

The presence of a continuous rapid ventricular response can induce left ventricular systolic dysfunction (i.e. tachycardia-induced cardiomyopathy). Furthermore, the takeover of atrial fibrillation with rapid ventricular response further impairs left ventricular filling through loss of active atrial contraction and shortening of diastole, leading to hypotension, which can in turn lead to patient discomfort and organ dysfunction [6].

Purpose of the Study and Methods:

We conducted a review of case reports in the literature on the administration of Landiolol in critically ill patients with acute decompensated heart failure (ADHF) secondary to tachyarrhythmias.

Due to off-label use, only 11 case reports/case series have been identified in this clinical setting.

11 cases have been identified [7,8,9,10,11] and all available data are reported in table 1. In addition to the clinical anamnestic data (Figure 1), a plot with the variations of the hemodynamic parameters over time is reported in figure 1. The heart rate and systolic pressure values e before and after the administration of Landiolol were plotted in the same summary in figure 1.

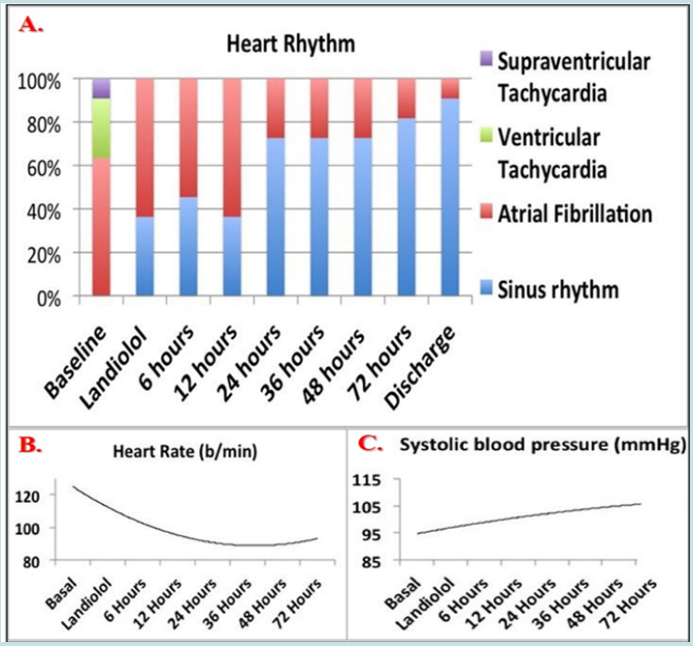

Figure 1: Hemodynamic trend of patients included in the case series review. Panel A: Arrhythmic profile over time and restoration of sinus rhythm. Box B: frequency trend line at baseline and after Landiolol infusion. Box C: trend line of systolic blood pressure over time (baseline, after infusion of Landiolol and up to 72 hours after the start of intravenous administration).

Results:

The mean age of the 11 patients was 55 years old with high proBNP values at admission.

The etiological diagnosis of heart failure was heterogeneous but tachyarrhythmia was the trigger event in all patients.

Patients were critically ill with a mean EF of 26 ± 16%. Were. ADHF was associated with septic shock in 4 of 11 patients, in 4 of 11 patients the clinical profile evolved into cardiogenic shock; 3 of 11 patients required intubation, 9 of 11 aminic inotropic support, and 3 of 11 required mechanical circulatory support.

Patients had a complex clinical profile, with depressed ejection fraction, hypotensive pressure profile, and non-sinus tachycardia. Landiolol administered together with other antiarrhythmic drugs (amiodarone in 4/11 patients), epinephrine/norepinephrine (9/11) and levosimendan (4/11) favoured heart rate lowering and an increase in systolic blood pressure.

At discharge, 4/11 had improved EF, in 10/11 sinus rhythm was restored, and all patients recovered hemodynamic stability without adverse events related to Landiolol).

All 11 patients survived with the restoration of hemodynamic stability (Table 1, Figure 1).

Table-1: Clinical profile, comorbidities, haemodynamic parameters, adverse events and clinical outcomes of the 11 patients included in the case-series review. Quantitative data are reported with +/- standard deviation. The qualitative data of the 11 patients are reported in fractions (n/N).

Clinical Profile of ADHF Patients Treated with Landiolol	
Age, (years±SD)	55,5±21
Sex	5/11
Weight, (kg±SD)	82±27
Cardiovascolar Profile	
Hypertension	5/11
Diabetes	2/11
History of Atrial Fibrillation	8/11
History of Ventricular Arrhythmias	3/11
Chronic Kidney Disease	4/11
Mean pro-BNP at admission (pg/mL±SD)	13500±9900
Acute Decompensated Heart Failure	11/11
Heart Failure Aetiologies	
Ischemic Cardiomyopathy	4/11
End-stage idiopathic dilated cardiomyopathy	3/11
Hypertrofic Cardiomyopathy	2/11
Tachycardiomyopathy	3/11
Clinical Status	
NYHA II	3/11
NYHA III-IV	8/11
Mean Ejection fraction at admission (%±SD)	26±16
Acute Pulmonary Edema	5/11
Septic Shock	4/11
Cardiogenic Shock	4/11
Orotracheal Intubation	3/11
Hemodynamic Profile at Admission	
Systolic blood pressure (mmHg±SD)	95±16
Mean blood pressure (mmHg±SD)	51±13

Heart rate (b/min±SD)	127±36
Hemodynamic Profile at Discharge	
Systolic blood pressure (mmHg±SD)	104±20
Heart rate (b/min±SD)	87±33
Cardiovascular Drugs	
Landiolol	11/11
Median Duration of Landiolol Infusion (24-72 hours), (hours)	72
Mean Landiolol dosage, (mg/kg/min±SD)	9±5
Amiodarone	4/11
Other oral beta blockers	9/11
Calcium Channel blockers	1/11
Dobutamine	4/11
Epinephrine / Norepinephrine	9/11
Levosimendan	4/11
Need for mechanical support (IABP, LVAD)	3/11
Need for renal replacement therapy	2/11
Adverse events from Antiarrhythmics	
Amiodarone toxicity (qt prolongation, torsades de pointes)	1/11
Hemodynamic instability from calcium channel blockers	1/11
Clinical Outcomes	
Improved Ejection fraction at discharge	4/11
Mean ejection fraction at discharge	33±15
Sinus rhythm restoration	10/11
Hemodynamic stability at discharge	11/11
Hospital survival	11/11

Discussion:

The high β1 selectivity of Landiolol is potentially useful in heart failure patients as first-line therapy for tachycardia and arrhythmia as it avoids the typical depression of cardiac function seen in other β-blockers. In this case series of complex patients with severe hemodynamic impairment, the overall balance appears favourable without relevant adverse events. Landiolol, thanks to its short half-life, respects the medical principle "Primum non-nocere", limits inappropriate tachycardia, and favours the restoration of sinus rhythm. Limiting the toxicity of catecholamines in the heart favours better pharmacological management of the patient in shock, especially in the era of mechanical support [12].

Despite the potential pharmacokinetic and pharmacodynamic profile of this new drug, the scientific evidence is still limited. Landiolol has been documented in randomized clinical trials of preventing postoperative atrial fibrillation in cardiac and non-cardiac surgery. Evidence on the prophylactic role of landiolol in the context of percutaneous coronary intervention and heart failure comes from small observational studies and requires further studies [13]. The theoretical combination of Landiolol with other inotropic drugs such as dobutamine, milrinone and levosimendan in the context of ADHF appears promising but randomized clinical trials or numerically significant observational studies are not yet available [14].

The limitations of our study and the limited evidence available in critically ill patients limit therapeutic assumptions. The indication of the drug in critically ill patients with septic / cardiac shock is still off-label and awaits further approvals.

Registries and randomized clinical trials will be needed for a better definition of the benefit-risk profile, in a critical clinical context where evidence is limited. But especially when the clinical risk is higher in terms of mortality, the higher may be the benefit [15].

Further studies are warranted to confirm the safety and efficacy of this pharmacological strategy in patients with decompensated heart failure [15].

Conclusion:

In this case series review, Landiolol was a useful strategy in patients with ADHF refractory to conventional therapy by facilitating rate/rhythm control, limiting the toxicity of inotropic drugs and improving the hemodynamic profile.

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