ICU
MANAGEMENT & PRACTICE
INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY
VOLUME 21 - ISSUE 5 - 2021

Microbiome in Critical Illness

9 771377 756005 04

Management of Acute Arrhythmias in Patients With Cardiac Dysfunction - Update of ESC Guidelines

In 2020, the ultra-short acting beta-blocker landiolol was first included in the ESC guidelines with a class I recommendation. The recommendations were based on study results demonstrating the rapid response, efficacy, and safety of this drug. At a recent symposium, during 2021 Heart Failure World Congress, cardiologists were invited to present their daily clinical practice of landiolol use.

The discovery of propranolol in 1964 by British pharmacologist Sir James Whyte Black laid the foundation for one of the pillars of cardiovascular therapy. "It would be easy to assume that since then, there has been nothing new to report in this family of drugs – but every now and then some offspring manages to surprise us, such as landiolol", says Prof Robert Hatala, from the National Cardiovascular Institute and Slovak Medical University, Bratislava (Slovakia).

Highly Selective, Ultra-Short Acting, Good Safety Profile

Prof Helmut Pürerfellner MD, Head of the Rhythmology Department at the Hospital Ordensklinikum Elisabethinen in Linz, Upper Austria, presented the unique features of landiolol: Landiolol is an innovative, highly selective β1-adrenergic receptor antagonist with the highest receptor selectivity of all beta-blockers, namely β1:β2 = 255:1; a short half-life of four minutes and a low volume of distribution. "A lower dose is therefore required to achieve a given plasma concentration, which in turn implies less distribution to tissues and fewer possible toxicities", the cardiologist explains. The onset of action is rapid with less than one minute, the duration of action is short with 10 to 15 minutes, resulting in a good controllability. Steady state is reached after 15 minutes under continuous i.v. infusion, or after two to five minutes after infusion of a loading dose (also possible as bolus) (Nasrollahi-Shirazi et al. 2016; DiPiro 2010; Alpert et al. 2014; Chow et al. 1996; Metoprolol SmPC).

Why is cardioselectivity important? For patients in critical condition "it is important to reduce the heart rate to minimise oxygen consumption while at the same time maintaining cardiac contractility", Prof Pürerfellner elaborates. As innovative beta-blocker molecule, landiolol has limited effect on Ca^{2+} and Na^{+} currents during action potential in cardiomyocytes, "allowing for the stability of stroke volume and blood pressure". Vasculature and bronchi need to be dilated so that the patient receives the maximum amount of oxygen. "All of this is possible with landiolol, thanks to the selective blockade of cardiac β1-receptors." Landiolol is therefore especially beneficial for patients with renal failure (rapid inactivation, no dose adjustment), liver impairment (CYP450 not involved in metabolisation), and lung comorbidities (prevention of bronchoconstriction) (Balik et al. 2018; SmPC Rapibloc). Other advantages include the missing potential for tolerance and the lack of a rebound phenomenon when using landiolol (Nasrollahi-Shirazi et al. 2016).

Effective Heart Rate Reduction Without Decreases of Blood Pressure

What do the clinical data say?

- Safety profile: A prospective observational study on approximately 1100 patients with cardiac dysfunction showed a low rate of adverse drug reactions under landiolol (5.6%) and a rate of <1% of severe bradycardia or hypotension. A good effect on heart rate (defined as ≥20% reduction) was seen in close to 80% of patients; in 888 patients 33.7% achieved cardioversion to sinus rhythm, the median time to cardioversion was 14 hours (Yamashita et al. 2019).
- Similar effects were observed in the J-Land study investigating landiolol vs. digoxin; the primary endpoints were defined as heart rate (HR) of <110 bpm and a >20% decrease of HR after two hours (Nagai et al. 2013). In this respect, landiolol was more effective (48.0% vs. 13.9%), and the safety profile was neutral.
- In patients with acute decompensated heart failure (ADHF), landiolol resulted in a decrease of HR from 141 beats/min (bpm) to 99 after six hours, without a significant decrease of systolic blood pressure vs. baseline (Kakihana et al. 2020).
- In patients with sepsis and persistent tachyarrhythmia, landiolol was compared to antiarrhythmics class I, II, III, IV and digitalis. Under landiolol, the multicentre (54 hospitals), open-label, randomised-controlled

trial showed a higher proportion of patients with low HR of 60-94 bpm (55% vs 33%) after 24h and a lower proportion of patients with new-onset arrhythmia after 168h (9% vs 25%) (Kakihana et al. 2020).

Guidelines: Short-Acting Beta-Blockers Preferable in Haemodynamic Instability

How these findings were incorporated in the current guidelines was the topic of the lecture given by Prof Zlatko Fras MD, Department for Vessel Diseases at the Medical University Center Ljubljana, Slovenia. The European Heart Rhythm Association (EHRA) for instance recommends cardioversion for the acute management of critically ill patients with arrhythmia and haemodynamic instability. Beta-blockers are recommended for haemodynamically stable patients, in case of risk of haemodynamic instability "short-acting beta-blockers may be preferred" (Boriani et al. 2019). In turn, the ESC guidelines for the management of atrial fibrillation (AF) published in 2020 recommend beta-blockers, diltiazem, or verapamil in LVEF ≥40% as first-line therapy; beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF <40%; in patients with haemodynamic instability or severely depressed LVEF, intravenous amiodarone may be considered for acute control of heart rate (Hindricks et al. 2020). "The most important thing in these guidelines however is the first-time inclusion of landiolol", the Slovenian expert stresses. "It is the only agent with a clear dose recommendation in patients with cardiac dysfunction, in particular dosages of 1µg/kg/min up to 10µg/kg/min. A higher dosage is of course possible without cardiac dysfunction."

Prof Fras then illustrates the use of landiolol in clinical practice with the help of a case report. An 82-year-old female patient with multiple pre-existing vascular diseases, comorbidities (including history of pulmonary oedema during amiodarone infusion) and polypharmacy presents with paroxysmal AF. The intervention consists of landiolol in a dosage of 1-7µg/kg/min. After close to six hours, the patient cardioverted into sinus rhythm, target HR was achieved "fairly quickly", and at discharge the patient was haemodynamically stable. "Landiolol was very effective, and in this situation, it was clearly the drug of choice", Prof Fras summarises.

> **"landiolol is an innovative, highly selective β1-adrenergic receptor antagonist with the highest receptor selectivity of all beta-blockers, a short half-life and a low volume of distribution"**

Landiolol

Landiolol is indicated in supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. It is also indicated in non-compensatory sinus tachycardia, where in the physician's judgement the rapid heart rate requires specific intervention. In patients with impaired left ventricular function (<40%), lower doses starting from 1µg/kg/min have been used.

Take-Home Messages From the ESC Guidelines

- Landiolol is the only beta-blocker with a specific dose recommendation for patients with cardiac dysfunction and acute AF.
- Landiolol has a class I recommendation: Evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective, the agent is therefore recommended or indicated.
- By contrast, amiodarone has class IIb, meaning usefulness/efficacy is less well established by evidence/opinion. The drug may be considered in patients with haemodynamic instability and severely depressed LVEF for acute control of heart rate. ■

References

Alpert JS et al. (2014) AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. J Am Coll Card, 64(21).

Balik M et al. (2018) Landiolol for managing post-operative atrial fibrillation. Eur Heart J Suppl, 20(Suppl A):A10-A14.

Boriani G et al. (2019) Management of Arrhythmias and Cardiac Electronic Devices in the Critically Ill and Post Surgery Patient. Europace, 21, 7-8.

Chow MS (1996) Intravenous amiodarone: pharmacology, pharmacokinetics, and clinical use. Ann Pharmacother, 30(6):637-43.

DiPiro JT (2010) Concepts in Clinical Pharmacokinetics. Lesson 1: Introduction to Pharmacokinetics and Pharmacodynamics, 1-19. ASHP.

Hindricks G et al. (2021) ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J, 42(5):373-498.

Kakihana Y (2020) Efficacy and safety of landiolol, an ultra-short-acting β1-selective antagonist, for treatment of sepsis-related tachyarrhythmia (J-Land 3S): a multicentre, open-label, randomised controlled trial. Lancet Respir Med, 8(9):863-872.

Matsui Y et al. (2019) Effects of Intravenous Landiolol on Heart Rate and Outcomes in Patients with Atrial Tachyarrhythmias and Acute Decompensated Heart Failure: A Single-Center Experience. Drugs - Real World Outcomes 6, 19–26

Metoprolol SmPC (2019) Available from mri.cts-mrp.eu/human/downloads/DE_H_3584_001_FinalSPC.pdf

Nagai R et al. (2013) Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short-acting β1-selective blocker landiolol with digoxin (J-Land Study). Circ J, 77(4):908-16.

Nasrollahi-Shirazi S et al. (2016) Comparison of the ß-Adrenergic Receptor Antagonists Landiolol and Esmolol: Receptor Selectivity, Partial Agonism, and Pharmacochaperoning Actions. J Pharmacol Exp Ther, 359(1):73-81.

SmPC Rapibloc (2017) Available from https://mri.cts-mrp.eu/Human/Downloads/NL_H_3368_002_FinalSPC.pdf

Yamashita T et al. (2019) A prospective observational survey on landiolol in atrial fibrillation/atrial flutter patients with chronic heart failure - AF-CHF landiolol survey. J Cardiol, 74(5):418-425.