Review Article

Landiolol Hydrochloride : A new β-blocker on the Block

Ramadoss R[1]

Abstract

Background : β-blocker group of drugs is well known for their role in cardiovascular diseases. Among these drugs, the short-acting group is mainly used for arrhythmias. Though heart rate is reduced by these drugs during arrhythmias, the concomitant reduction in blood pressure is an unfavourable side effect in some instances. A new drug, Landiolol, an ultra-short acting β1 blocker has been developed and is being used in Japan and Europe. It is a highly selective β1 receptor blocker that does not cause a significant reduction in blood pressure. This educational forum article is about this new drug which is being used in many arrhythmia-related conditions.

Key words : Landiolol, β-blockers, Arrhythmias, Atrial fibrillation.

β adrenergic receptor antagonists, commonly known as β-blockers, exert their function by blocking β1 and β2 sympathetic receptors predominantly located in the heart and smooth muscles respectively. They are classified into cardioselective (relatively selective for β1 receptors) and non-cardio selective blockers (blocks both β1 and β2). This group of drugs is commonly used in cardiovascular diseases. Being an effective anti-arrhythmic, β-blockers are used as first-line therapy for tachyarrhythmias.

β-blockers used for arrhythmias include Esmolol, Metoprolol succinate and Sotalol. Among these drugs, Esmolol is the shortest acting. But, in addition to the negative chronotropic effect, Esmolol exerts significant negative inotropic effort causing a decrease in cardiac contractility and blood pressure. Hence Landiolol Hydrochloride was developed, which has a less negative effect on blood pressure and cardiac contractility as compared to Esmolol[1]. This drug has been in use in Japan for more than 15 years. It has been recently approved in Europe for rate control in Atrial Fibrillation[2].

Editor's Comment :

- Landiolol is an ultra-short-acting β1-antagonist.
- It has less effect on cardiac contractility and causes less variation in blood pressure.
- It can be used as a better alternative to Esmolol in the management of peri-operative tachyarrhythmias, atrial fibrillation and sepsis-related tachyarrhythmias.

Mechanism of Action :

Landiolol is an ultra-short acting highly selective β1 antagonist. It inhibits the action of catecholamines (Adrenaline and Nor-adrenaline) through β1 receptors and reduces the sympathetic drive. This results in a reduction of heart rate, decreased spontaneous firing of ectopic pacemakers, slows the conduction and increases the refractory period of the AV node. The expected consequences of this action are a reduction in myocardial contractility and a fall in blood pressure. But, Landiolol, being a highly selective β1-blocker, has less effect on blood pressure and a more potent negative chronotropic effect. It was found in animal studies that it has a very high selectivity for the β1 receptor (β1: β2=255:1). This ratio is significantly higher than that of Esmolol (33 times)[3]. Landiolol is 100 times cardio-specific than Metoprolol. Unlike some other β-blockers, Landiolol does not have any membrane-stabilizing activity or intrinsic sympathomimetic activity in vitro[4].

The half-life of Landiolol is shorter compared to Esmolol (4 minutes *versus* 9 minutes). So, the heart rate reaches baseline within 30 minutes of discontinuing the infusion and hence the dose is easily titratable[1].

Pharmacokinetics :

Unlike Esmolol, Landiolol is a pure S-enantiomer and it has an ester in its structure[5]. Landiolol is metabolized in plasma and liver by pseudocholinesterase and carboxylesterase, respectively. Metabolites are in carboxylate and benzoic forms. It is excreted mainly in the metabolite form and less than 10% as an unchanged drug via urine. Almost all the administered dose (99%) is excreted within 24 hours. Landiolol and its metabolites do not inhibit cytochrome P450 isoenzymes[1].

[1]MD, Associate Professor, Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry 605006 and Corresponding Author

Received on : 13/06/2022
Accepted on : 22/01/2023

How to cite this article : Landiolol Hydrochloride : A new β-blocker on the Block. Ramadoss R. *J Indian Med Assoc* 2025; **123(7):** 47-9.

Though metabolites of Landiolol are excreted mainly through kidneys and are likely to get accumulated in case of renal impairment, the β-blocking activity of metabolites is very weak when compared to the parent drug. In hepatic dysfunction, half-life and elimination are found similar to that of healthy individuals. Hence in patients with renal and hepatic impairment, no dose adjustment is recommended for Landiolol. But caution is recommended as the data is limited[6]. Following pharmacokinetic data of Landiolol had been reported after infusing it to five healthy volunteers at the rate of 0.04 mg/kg/min for 60 min: Clearance (ml/kg/min)- 41.8, volume of distribution (ml/kg)- 242, half-life (min) 3.96 and Cmax (mcg/ml) - 1.01.[1]

Clinical Trials :

A study conducted by Yamakage, *et al* on guinea pigs and humans concluded that both Esmolol and Landiolol did not cause broncho-constriction through β2 receptors situated in bronchial smooth muscles and they could be safely used in patients with airway hyperreactivity[7]. Effect of Landiolol on heart rate in patients undergoing reperfusion therapy for the acute coronary syndrome was studied in 22 patients in Japan by Hoshi, *et al.* There was a statistically significant decrease in mean heart rate (from 87 to 72 beats/min) after 20 minutes of starting the drug with an initial dose of 20 mcg/kg/min. Blood pressures remained unchanged during Landiolol infusion[8].

Digoxin and Landiolol were compared in a study (J-Land study) to achieve a primary endpoint of a decrease in heart rate to <110/min and >20% reduction at 2 hours in patients having atrial fibrillation/ atrial flutter with cardiac failure (Ejection fraction- 25-50%). Landiolol arm achieved target heart rate better than digoxin (48% *versus* 14%, P<0.001)[9]. Postoperative arrhythmias are more common after cardiovascular surgeries. Landiolol was proven to control those arrhythmias. In a randomised, double-blind, placebo-controlled trial, the occurrence of atrial fibrillation after 1 week of coronary artery bypass grafting was observed after giving Landiolol infusion (2mcg/kg/min) for 48 hours after surgery. Atrial fibrillation was significantly less in the Landiolol group (10% *versus* 34.3%)[10]. Landiolol was found to be the better beta blocker to prevent postoperative atrial fibrillation in a meta-analysis[11].

An open-label pilot study was conducted in Vienna in which 20 outpatients who presented with atrial fibrillation were treated with Landiolol. Heart rate was reduced in all patients and 85% of the patients had symptomatic improvement. Three patients developed hypotension which was reversed by stopping the drug[12]. Tachycardia after intubation is more common. Landiolol was tested in a placebo-controlled randomised trial for its effects on heart rate after intubation. The baseline heart rate of the Landiolol group and placebo group was 62 and 65 beats/min respectively. Patients receiving the drug had significantly less variation in heart rate from the baseline after the procedure compared to the placebo group (71 *versus* 102 beats/min). Mean arterial pressure changes from baseline was also less in Landiolol group (39% *versus* 55%)[13] (Table 1).

Sepsis is well known to cause tachycardia and arrhythmia due to inflammation. Inotropic drugs used for septic shock may also contribute to tachyarrhythmias. A multicentre, open-label, randomised control trial was conducted in Japan to study the efficacy of Landiolol in patients with septic shock requiring catecholamine support and having sinus tachycardia, atrial fibrillation or atrial flutter with a minimum heart rate of 100 beats/min. The primary endpoint (heart rate reduction to 60-94/min at 24 hours) was achieved in the Landiolol group better than in the control group (55% *versus* 33%). Nine patients (12%) developed hypotension in the Landiolol group which was managed by reducing the dose or discontinuing the drug[14].

The drug has been in use in Japan since 2002 under the brand name of 'Onoact'. It was approved in Europe

Table 1 — *Clinical uses and dosage of Landiolol*

Indications[15]	Loading dose	Maintenance dose	Remarks
Intra-operative tachyarrhythmia (Atrial fibrillation, Atrial flutter, sinus tachycardia)	0.125 mcg/kg/min For 1 minute	0.04 mcg/kg/min	Heart rate and BP to be monitored.
Postoperative tachyarrhythmia (Atrial fibrillation, Atrial flutter, sinus tachycardia)	0.06 mcg/kg/min	0.02 mcg/kg/min	Heart rate and BP to be monitored.
Atrial fibrillation and Atrial flutter in deteriorated cardiac function	-	1 mcg/kg/min	Titrate between 1-10 mcg/kg/min
Ventricular fibrillation and hemodynamically unstable ventricular tachycardia	-	1 mcg/kg/min	Titrate between 1-10 mcg/kg/min. Dose can be increased till 40 mcg/kg/min if recurrent.

in 2016 where it is available under different brands such as Rapibloc, Landiobloc, Runrapiq, Raploc. It is not yet approved by the US FDA.

Conclusion

Landiolol, being an ultra-short-acting β1- antagonist, has a rapid onset of action and is easily titratable. Its adverse effects, if any, can be quickly reversed. When compared to Esmolol, it has less effect on cardiac contractility and hence causes less variation in blood pressure. Hence, Landiolol can be used as a better alternative to Esmolol in the management of peri-operative tachyarrhythmias, atrial fibrillation in heart failure and in intubation and sepsis-related tachyarrhythmias. This agent is used widely in Japan for various conditions and has been recently approved in Europe for the treatment of atrial fibrillation. It is high time the drug is made available in India after conducting necessary trials.

Funding : None

Conflict of Interest : None

References

1 Plosker GL — Landiolol: a review of its use in intraoperative and postoperative tachyarrhythmias. *Drugs* 2013; **73:** 959-77.
2 Gerhard Hindricks G, Potpara T, Dagres N, Arbelo E,Bax JJ, m-Lundqvist CB — 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020; **00:** 1-125. doi:10.1093/eurheartj/ehaa612
3 Nasrollahi-Shirazi S, Sucic S, Yang Q, Freissmuth M, Nanoff C — Comparison of the β-adrenergic receptor antagonists landiolol and esmolol: receptor selectivity, partial agonism, and pharmacochaperoning actions. *J Pharmacol Exp Ther* 2016; **359:** 73-81.
4 Syed YY — Landiolol: A Review in Tachyarrhythmias. *Drugs* 2018; **78(3):** 377-88.
5 Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, *et al* — Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. *Chem Pharm Bull (Tokyo)* 1992; **40:** 1462-9.
6 Rapibloc — Summary of product characteristics. Accessed on 08/12/2020. https://mri.cts-mrp.eu/Human/Downloads/NL_H_3368_002_FinalSPC.pdf.
7 Yamakage M, Iwasaki S, Jeong S-W — Beta-1 selective adrenergic antagonist landiolol and esmolol can be safely used in patients with airway hyperreactivity. *Heart Lung* 2009; **38(1):** 48-55.
8 Hoshi T, Sato A, Nishina H, Kakefuda Y, Wang Z, Noguchi Y, *et al* — Acute hemodynamic effects of landiolol, an ultra-short-acting beta-blocker, in patients with acute coronary syndrome: Preliminary study. *Journal of Cardiology* 2012; **60(4):** 252-6.
9 Nagai R, Kinugawa K, Inoue H, Atarashi H, Seino Y, Yamashita T, *et al* — Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultrashort- acting beta1-selective blocker landiolol with digoxin (J-Land study). *Circ J* 2013; **77:** 908-16.
10 Sezai A, Minami K, Nakai T — Landiolol hydrochloride for prevention of atrial fibrillation after coronary artery bypassgrafting: new evidence from the PASCAL trial. *J Thorac Cardiovasc Surg* 2011; **141(6):** 1478-87.
11 Masuda Y, Luo HD, Kang GS, Teoh KLK, Kofidis T — Meta-analysis of the benefit of beta-blockers for the reduction of isolated atrial fibrillation incidence after cardiac surgery. *JTVCS Open* 2020; **3:** 66-85.
12 Stix G, Wolzt M, Domanovits H, Kadlecova P, Husch B, Trebs M, *et al* — Open-Label Two-Dose Pilot Study of Landiolol for the Treatment of Atrial Fibrillation/Atrial Flutter in Caucasian Patients. Circulation Journal, Article ID CJ-19-0661. Accessed on 08/12/2020. https://www.jstage.jst.go.jp/article/circj/advpub/0/advpub_CJ-19-0661/_html/-char/en.
13 Kawano T, Eguchi S, Iseki A — Effects of landiolol on cardiovascular responses, bispectral index and body movement during endotracheal intubation (in Japanese). *Jpn J Anesthesiol* 2005; **54(6):** 610-4.
14 Kakihana Y, Nishida O, Taniguchi T, Okajima M, Morimatsu H, Ogura H, *et al* — Efficacy and safety of landiolol, an ultra-short-acting â1-selective antagonist, for treatment of sepsis-related tachyarrhythmia (J-Land 3S): a multicentre, open-label, randomised controlled trial. *The Lancet Respiratory Medicine* 2020; **8(9):** 863-72.
15 A short acting selective β1 blocker. ONOACT® for intravenous infusion 50mg/150mg approved for additional indication of ventricular arrhythmia in Japan. Accessed on 08/12/2020. https://www.ono.co.jp/eng/news/pdf/sm_cn190326.pdf.