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Landiolol: pharmacology and its use for rate control in atrial fibrillation in an emergency setting

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This article provides new insight on landiolol, an ultra-short acting injectable betablocker, recently approved in Europe, with regard to its pharmacokinetic and pharmacodynamic profile, along with its first experience in Caucasian healthy volunteers and patients with atrial fibrillation. Landiolol as iv formulation exhibited in an emergency setting rapid rate reduction in patients with tachycardic atrial fibrillation without pronounced blood pressure drop both in caucasian and asian populations in similar manner.

Pharmacology of landiolol in humans and animal models

Landiolol is an ultra-short acting, I.V. β1-blocker that has been available in Japan for 15 years for the treatment of supraventricular tachyarrhythmias, such as atrial fibrillation (AF), atrial flutter (AFL), and non-compensatory sinus tachycardia.[1] Landiolol shares similarities to esmolol, such as the metabolism pathway; however, landiolol presents faster pharmacokinetics, acts with higher 'potency', and enjoys higher cardioselectivity. Furthermore, unlike esmolol, landiolol has limited impact on blood pressure which proves to reduce the heart rate without undesired drop of arterial blood pressure.[1]

Landiolol is in contrast to esmolol a pure S-enantiomer, and its structure includes an ester-bound. It is rapidly metabolized in the plasma by pseudocholinesterases and carboxylesterases, but unlike esmolol, does not yield methanol production.[2]

When compared with esmolol in animal models, landiolol displayed a very high cardioselectivity (β1/β2-selectivity = 255:33)[2] which was consistently retrieved in another model (β1/β2-selectivity = 216:30).[3] This translates into a seven-fold higher cardioselectivity for landiolol over esmolol.

Landiolol has an 8- to 12-fold potency when compared with esmolol. Doses used in clinical studies are 5–10 times lower for landiolol, ranging from less than 5 mcg/kg/min up to 40 mcg/kg/min[1] while esmolol doses usually range from 25 mcg/kg/min up to 300 mcg/kg/min (molecular weight of esmolol hydrochloride and landiolol hydrochloride are 332 g/mol and 546 g/mol, respectively).[4]

In isolated rabbit hearts, landiolol and esmolol showed negative chronotropic effects, whereas landiolol exhibited a less potent negative inotropic effect compared to esmolol.[5] The weaker negative inotropic effect was confirmed using isolated perfused guinea pig hearts.[6] In addition, the same team using isolated myocyte and patch-clamp techniques showed that esmolol inhibited both the inward rectifier K+ current and the L-type Ca2+ current, and increased the outward current dose-dependently. In contrast, landiolol had minimal cardiac myocyte effects.[6]

In rabbits, landiolol appears to have a more potent negative chronotropic effect and a less blood pressure lowering effect following a dosage increase, and a shorter half-life than esmolol.[7]

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In the same experiment, renal sympathetic nerve activity (RSNA) remained unchanged with landiolol but increased in a dose-dependent fashion with esmolol, suggesting a reflex increase in RSNA in response to the dose-dependent reduction of blood pressure.[7]

Clinical dose response and pharmacokinetics in the Asian and Caucasian population

Pharmacodynamic characteristics of landiolol established in animals were confirmed in humans, both in heathly volunteers and clinical trials.[8,9,10-15]

In healthy Caucasian volunteers, more profound effects on the heart rate were observed after landiolol infusion compared to esmolol; the latter displayed a more prolonged hypotensive effect when infused at equipotent doses.[8,9]

In patients anesthetized for surgery, plasma renin activity (PRA) was found to be significantly decreased by 25% by pre-treatment with esmolol while no significant effect was seen with landiolol on PRA.[10]

The doses used to control heart rate were evaluated in several Phase II and Phase III trials[11-15] which determined that a loading dose of 0.125 mg/kg for 1 min followed by an infusion titrated from 10 to 40 mcg/kg/min, with a maximum of 80 mcg/kg/min is most beneficial.

As landiolol was also used as a bolus dose of 0.1 mg/kg to control heart rate during surgery,[16] the loading dose in the European approved label is 0.1 mg/kg to 0.3 mg/kg.[17]

The formulation of landiolol (300 mg in 50 mL) with a 6 mg/mL concentration facilitates easier dosing. The concentration being a multiple of 60 min, dose in mcg/kg/min can easily translate into flow rate ml/hour, which nurses usually utilize in intensive care. Thus, initial infusion maintenance dose (10 mcg/kg/min) can be easily obtained from the patient weight divided by 10 (70 kg/10 = 7 ml/hr).

Higher doses (20–40 mcg/kg/min up to 80 mcg/kg/min) are required for treating intra-operative paroxysmal supraventricular tachycardia (PSVT), sinus tachycardia,[11-14] and patients in an emergency department setting (H. Domanovits *et al.*, unpublished data),[15,16] than those suitable to control heart rate of patients with perioperative AF[18] and patients with AF and cardiac dysfunction managed in cardiac[19] and intensive care units[20] (5–10 mcg/kg/min). The use of landiolol in these settings will be covered by other articles of this supplement,[21-24] while experience in the emergency department setting will be described below. A dose ranging study[14] evaluating landiolol efficacy and safety to control heart rate of supraventricular tachycardia in an emergency department compared three dose regimens: Low (0.063 mg/kg loading +20 mcg/kg/min), Moderate (0.125 mg/kg loading +40 mcg/kg/min), and High (0.250 mg/kg loading +80 mcg/kg/min). Response rates were 55.6% in Group Low, 61.9% in Group Moderate, and 69.2% in Group High in patients with AF or AFL, whereas in other PSVT they were 47.1% in Group Low, 57.1% in Group Moderate, and 47.4% in Group High. The same team[15] consequently compared most effective dose High (0.250 mg/kg loading +80 mcg/kg/min) to placebo focusing on patients with AF or AFL. This study showed that

Table 1 Landiolol pharmacokinetics

Pharmacokinetic parameters	Japanese population[1]	Caucasian population[8,9]
CL (mL/kg·min)	41.8	52.8
VD (mL/kg)	242	366
$t_{1/2}$ (min)	3.96	4.52
C_{max} (mcg/mL)	1.01	0.98

CL, clearance; VD, volume of distribution.

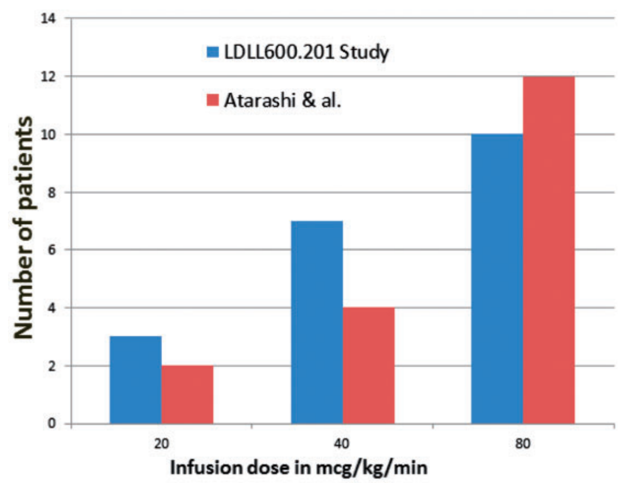

Figure 1 Dose response in patients with supraventricular tachycardia treated with landiolol in the emergency department.

landiolol was able to control tachycardia and significantly improve symptoms in 62.2% (28 of 45 patients) compared to only 2.3% (1 of 44 patients) in the placebo group. The incidence of adverse events did not significantly differ between landiolol and placebo, with an incidence of 8.0% (4 of 50 patients) and 14.3% (7 of 49 patients), respectively.

The pharmacokinetic profile of landiolol has been determined in the Caucasian[8,9] and found similar to the Asian population (*Table 1*).

Experience in Caucasian patients with atrial fibrillation

Our team has evaluated landiolol safety, tolerability, pharmacokinetics, and pharmacodynamics of landiolol in Caucasian patients with tachycardic AF/AFL treated in an emergency department. We tested two different regimens: the conventional dosing scheme, starting with a loading infusion of 100 mcg/kg/min over 1 min, followed by a 40 mcg/kg/min infusion in 10 patients. The alternative dosing scheme started directly with a 40 mcg/kg/min continuous infusion, with the possibility to titrate up and down according to patient response.

We found that both regimens provided similar efficacy with 76% of AF patients achieving a target heart rate below 100 b.p.m. All patients were relieved of symptoms (rapid heartbeat, shortness of breath, sweating, palpitation, and dizziness), and 90% were relieved of fatigue and irregular pulse. Mean arterial pressure remained above −10% of baseline during the landiolol infusion. Landiolol was well tolerated by all but three patients with rapidly reversible transient hypotension.

Dose response in Caucasian patients showed a similar pattern as in Asian patients treated for the same conditions in an emergency department, as shown by Atarashi *et al.*[25] (*Figure 1*).

Conclusion

In conclusion, the ultra-short acting and highly beta-1 selective compound landiolol exhibits profound negative chronotropic and weak negative inotropic effects as well as a limited impact on blood pressure. These characteristics make it suitable for critical care purposes, where patient instability is a frequent concern. The easy dosing and titrability of landiolol as well as its safety are advantages to improve patient management in this setting. Landiolol response and success rates and pharmacodynamic and pharmacokinetic characteristics have been shown to be similar in the Caucasian and Asian population. The experience with Landiolol gathered in Japan could help European clinicians to incorporate landiolol in their strategy to manage patients with tachycardic AF.

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References

1. Plosker GL. Landiolol: a review of its use in intraoperative and postoperative tachyarrhythmias. *Drugs* 2013;**73**:959–977.
2. Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, Sakaki K, Hachiya K, Ichioka Y, Kawamura M. Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. *Chem Pharm Bull (Tokyo)* 1992;**40**:1462–1469.
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. Garnock-Jones KP. Esmolol: a review of its use in the short-term treatment of tachyarrhythmias and the short-term control of tachycardia and hypertension. *Drugs* 2012;**72**:109–132.
5. Ikeshita K, Nishikawa K, Toriyama S, Yamashita T, Tani Y, Yamada T, Asada A. Landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts. *J Anesth* 2008;**22**:361–366.
6. Shibata O, Nishioka K, Yamaguchi M, Makita T, Sumikawa K. High concentrations of landiolol, a beta(1)-adrenoceptor antagonist, stimulate smooth muscle contraction of the rat trachea through the Rho-kinase pathway. *J Anesth* 2008;**22**:21–26.
7. Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth* 2001;**48**:985–989.
8. Krumpl G, Ulč I, Trebs M, Kadlecová P, Hodisch J, Maurer G, Husch B. Pharmacodynamic and -kinetic behavior of low-, intermediate-, and high-dose landiolol during long-term infusion in Whites. *J Cardiovasc Pharmacol* 2017;**70**:42–51.
9. Krumpl G, Ulc I, Trebs M, Kadlecová P, Hodisch J. Bolus application of landiolol and esmolol: comparison of the pharmacokinetic and pharmacodynamics profiles in a healthy Caucasian group. *Eur J Clin Pharmacol* 2017;**73**:417–428.
10. Kakuta N, Kawano T, Tanaka K, Oshita S. A comparison of landiolol and esmolol for attenuation of cardiovascular response and plasma renin activity against tracheal intubation with laryngoscopy. *Anesthesiology* 2005;**103**:A433.
11. Yoshiya I, Ogawa R, Okumura F, Shimada Y, Hanaoka K. Clinical evaluation of landiolol hydrochloride (ONO-1101) on perioperative supraventricular tachyarrhythmia—a phase III, double-blind study in comparison with placebo (in Japanese). *Rinsho Iyaku* 1997;**13**: 4949–4978.
12. Taenaka N, Kikawa S. The effectiveness and safety of landiolol hydrochloride, an ultra-short-acting β1-blocker, in postoperative patients with supraventricular tachyarrhythmias: a multicenter, randomized, double-blind, placebo-controlled study. *Am J Cardiovasc Drugs* 2013;**13**:353–364.
13. Taenaka N, Kikawa S. Dose-dependent effect of landiolol, a new ultra-short-acting β(1)-blocker, on supraventricular tachyarrhythmias in postoperative patients. *Clin Drug Investig* 2013;**33**:505–514.
14. Kato K, Hayakawa H, Atarashi H, Sugimoto T, Inoue H, Hiejima K, Ogawa S, Iinuma H, Nakata Y, Tanabe T, Kasanuki H. Clinical trial of an ultra short acting β1-blocker; landiolol hydrochloride (ONO-1101), on paroxysmal atrial fibrillation or flutter and paroxysmal supraventricular tachycardia–an open label, dose finding study (Late Phase II Study). *Rinsho Iyaku* 1997;**13**:4873–4901.
15. Kato K, Hayakawa H, Atarashi H, Sugimoto T, Inoue H, Hiejima K, Ogawa S, Iinuma H, Nakata Y, Tanabe T, Kasanuki H, Hanaoka K. Clinical effect of intravenous infusion of landiolol hydrochloride (ONO-1101) on paroxysmal atrial fibrillation and atrial flutter: a phase III, double-blind study in comparison with placebo [in Japanese]. *Rinsho Iyaku* 1997;**13**:4903–4924.
16. Inoue S, Tanaka Y, Kawaguchi M, Furuya H. The efficacy of landiolol for suppressing the hyperdynamic response following laryngoscopy and tracheal intubation: a systematic review. *Anaesth Intensive Care* 2009;**37**:893–902.
17. RAPIBLOC (landiolol hydrochloride) summary of product characteristics—NL/H/3368/001-003/DCBH/VDA/ALA/DNS. http://www.amomed.com/product/rapibloc-2/?lang=en.
18. Sakamoto A, Hamasaki T, Kitakaze M. Perioperative landiolol administration reduces atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials. *Adv Ther* 2014;**31**:440–450.
19. Nagai R, Kinugawa K, Inoue H, Atarashi H, Seino Y, Yamashita T, Shimizu W, Aiba T, Kitakaze M, Sakamoto A, Ikeda T, Imai Y, Daimon T, Fujino K, Nagano T, Okamura T, Hori M; J-Land Investigators. 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* 2013;**77**:908–916.
20. Yoshida Y, Terajima K, Sato C, Akada S, Miyagi Y, Hongo T, Takeda S, Tanaka K, Sakamoto A. Clinical role and efficacy of landiolol in the intensive care unit. *J Anesth* 2008;**22**:64–69.
21. Fellahi JL, Heringlake M, Knotzer J, Fornier W, Cazenave L, Guarracino F. Landiolol for managing atrial fibrillation in post-cardiac. *Eur Heart J* 2018;**20**(Suppl A):A4–A9.
22. Balik M, Sander M, Trimmel H, Heinz G. Landiolol for managing post-operative atrial fibrillation. *Eur Heart J* 2018;**20**(Suppl A): A10–A14.
23. Von Haeling S, Bělohlávek J, Er F, Gassanov N, Guarracino F, Bouvet O. Landiolol for rate control management of atrial fibrillation in patients with cardiac dysfunction. *Eur Heart J* 2018;**20**(Suppl A): A19–A24.
24. Rehberg S, Joannidis M, Whitehouse T, Morelli A. Landiolol for managing atrial fibrillation in intensive care. *Eur Heart J* 2018;**20**(Suppl A): A15–A18.
25. Atarashi H, Kuruma A, Yashima M, Saitoh H, Ino T, Endoh Y, Hayakawa H. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000;**68**:143–150.