Effects of Landiolol Hydrochloride on Intractable Tachyarrhythmia After Pediatric Cardiac Surgery

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<tr>
<th>著者別名</th>
<th>徳永 千穂 ⓧ 平松 祐司 ⓧ 金本 真也 ⓧ 髙橋 実穂 ⓧ 堀米 仁志 ⓧ 檜原 謙</th>
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URL   | http://hdl.handle.net/2241/119455

doi: 10.1016/j.athoracsur.2013.01.057
Effects of Landiolol Hydrochloride on Intractable Tachyarrhythmia

After Pediatric Cardiac Surgery

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Running head: Landiolol for pediatric tachyarrhythmia

Keywords: arrhythmia, pediatric, congenital heart disease

Word Count: 2562 words

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Abstract

Background. While β-blockers can be effective in controlling tachyarrhythmias after pediatric cardiac surgery, a negative inotropic influence sometimes complicates their use. Landiolol hydrochloride is a novel, ultra-short-acting β-blocker recently developed in Japan. The drug has higher β1/β2 selectivity ratio and a less negative inotropic effect. This study retrospectively evaluates the efficacy and safety of landiolol in the management of tachyarrhythmias after pediatric cardiac surgery.

Methods. A retrospective analysis was performed on 312 consecutive patients undergoing surgery for congenital heart disease. Twelve patients were treated with landiolol for critical tachyarrhythmia. The mean age of patients was 28.7 ± 10.6 months. Five junctional ectopic tachycardia, 2 atrial flutters, 1 paroxysmal supraventricular tachycardia, 1 atrial fibrillation, 1 atrioventricular reciprocating tachycardia with Wolff-Parkinson White Syndrome and 2 excessive sinus tachycardia were treated.

Results. The mean loading and maintenance doses were 11.3 ± 4.0 and 6.8 ± 0.9 μg/kg/min, respectively. Rate control was achieved in all patients. Landiolol reduced the heart rate from 169.7 ± 11.4 to 127.7 ± 7.5 bpm (p<0.05) while blood pressure did not significantly change. Tachyarrhythmias were converted to sinus rhythm in 70.0% of the cases and the average time
needed to achieve heart rate reduction was 2.3 ± 0.5 hours.

**Conclusions.** Landiolol was efficacious in treating tachyarrhythmia in pediatric cardiac surgery. The desired negative chronotropic effect was achieved without significant hemodynamic compromise. The ultra-short half-life of landiolol provided rapid dose manipulation. This study suggests that landiolol is a promising option for the management of postoperative tachyarrhythmias in pediatric patients.

(255 words)
Intractable tachyarrhythmia after pediatric cardiac surgery can quickly lead to hemodynamic instability and requires prompt management. While β-blockers can be effective in controlling these tachyarrhythmias, a negative inotropic influence sometimes complicates their use.

Landiolol hydrochloride (Ono Pharmaceutical Co, Ltd, Osaka, Japan) is a novel ultra-short-acting β-blocker developed in Japan. Plasma half-life of the drug is 4 minutes. It has a higher β1/β2 selectivity ratio and as a result a less pronounced negative inotropic effect compared with other intravenous β-blockers. Landiolol has become a common therapeutic option for the management of postoperative tachyarrhythmia in adult patients in Japan.

However, little has been reported regarding its use in pediatric patients. We report our experience with landiolol in postoperative pediatric cardiac surgical patients suffering from intractable tachyarrhythmia.

**Patients and Methods**

Between 2006 and 2012, 312 patients underwent open heart surgery for congenital heart disease at the Tsukuba University hospital. Twelve of these patients developed intractable tachyarrhythmia after surgery and were treated with landiolol. The study was approved by the University of Tsukuba Institutional Review Board and patient records were analyzed retrospectively.
In all patients tachyarrhythmia resulted in hemodynamic instability, and was treated with a standard protocol which included cooling for hyperthermia, sedation, electrolyte imbalance management and minimization of intravenous catecholamine infusion if possible.

In the earlier cases, the administration of landiolol was initiated at 40 μg / kg / min for loading and gradually decreased into the recommended maintenance dose of 10 to 40μg / kg / min according to the pharmaceutical reference. In later cases, the administration of landiolol was started with a relatively low dose at 3-5 μg / kg / min with special concern for excessive negative chronotropic effect with a loading of 40 μg / kg / min since we experienced one case that developed excessive bradycardia with the initial protocol. The maintenance dose of landiolol was settled at the lowest effective dose needed to sustain sinus rhythm or adequate heart rate with stabilized hemodynamics.

Statistical analysis

All values are expressed as the mean ± standard error of the mean. Statistical analysis was performed using the Wilcoxon signed-rank test to compare pre- and post-administration heart rate and systolic blood pressure. SPSS 19.0 for windows (SPSS Inc, Chicago, IL) was used for analyses.
Results

The characteristics of the 12 patients treated with landiolol are listed in Table 1. The mean age of patients was 28 ± 10 months (range, 10 days to 108 months). There were 5 junctional ectopic tachycardia (JET), 2 atrial flutter, 1 paroxysmal supraventricular tachycardia (PSVT), 1 atrial fibrillation, 1 atrioventricular reciprocating tachycardia (AVRT) by Wolff-Parkinson-White (WPW) syndrome and 2 excessive sinus tachycardia. Digoxin and lidocaine were used in 2 cases before the administration of landiolol.

The mean loading dose was 11.3 ± 4.0 μg / kg / min and the maintenance dose was 6.8 ± 0.9 μg / kg / min. Landiolol reduced the heart rate significantly from 169.7 ± 11.4 to 127.7 ± 7.5 beats / minute (Figure 1), while pre- and post-administration systolic blood pressure did not significantly change. The average time needed to achieve a 20% heart rate reduction was 2.3 ± 0.4 hours (Table 2).

Tachyarrhythmias were converted to regular sinus rhythms in 70 % of cases and the final average percent reduction in heart rate was 23.7 ± 4.2 %. One neonate among the earlier cases rapidly developed an excessive bradycardia with heart rate below 100 beats / min at 48 hours after the onset of landiolol infusion with 10.0 μg /
kg / min. Hemodynamic stability was reestablished by immediate cessation of landiolol and introduction of atrial pacing. Heart rate was maintained under atrial pacing without restart of landiolol.

Comment

The efficacy of β-blockade in treating tachyarrhythmia after cardiac surgery is widely recognized. Despite this the myocardial depressant effects of these drugs complicates their use.

Landiolol is a novel ultra-short-acting β-blockade which has a plasma half-life of 4 minutes. Landiolol was developed in Japan and released in 2002. In a recent randomized control study, Sezai et al. reported that landiolol administration significantly reduced the occurrence of atrial fibrillation and heart rate in patients after adult cardiac surgery without significant change in blood pressure. Another prospective multicenter randomized study in adult patients (JL-KNIGHT) was also recently undertaken in Japan. In this study, landiolol was effective for the conversion of atrial fibrillation to sinus rhythm after open heart surgery with a lower incidence of hypotension. The drug has been widely used in Japan and recognized as one of the useful options for the management of postoperative tachyarrhythmias in adult patients. However, until now the efficacy of landiolol in pediatric cardiac surgery patients has not been published. The present study reports our earliest experience.
β-adrenergic receptors are subdivided into two basic types. β1-receptors exist in the myocardium and their stimulation has both inotropic and chronotropic effects. β2-receptors exist in smooth muscle cells and their stimulation results in bronchodilation and vasodilation. β-blockades are characterized by the selectivity for β1 and β2 stimulation. There are 3 β-blockades available for intravenous injection at present. One is propranolol which has a low β1 / β2 selectivity ratio of 0.6 and a long plasma half-life of 120 min. Because of its strong negative inotropic effect and long half-life, propranolol is not the drug of choice for critical care after pediatric cardiac surgery. Esmolol hydrochloride is another β-blockade which has a higher β1 / β2 selectivity ratio of 20 and a plasma half-life of 9 minutes. Esmolol has been also commercially available in Japan since 2002. Compared with these intravenous β-blockades, landiolol has the shortest plasma half-life of 4 minutes and the highest β1 / β2 selectivity ratio of 277.

Ikeshita et al. reported that landiolol and esmolol had equipotent negative chronotropic effects. However, landiolol showed less of a negative inotropic effect including the maximal rate of left ventricular force development ($LVdP / dtmax$) while esmolol demonstrated a strong inhibitory effect $^{10, 11}$. In our cases, more than 20 % heart rate reduction was achieved in all
patients without decrease in blood pressure by landiolol. Also rhythm conversion was obtained in 70% of patients. These results are consistent with previous studies which demonstrate the strong negative chronotropic effect without negative inotropic effect of landiolol in adult patients after cardiac surgery\textsuperscript{7, 8}. Additionally, Shibata et al. reported that landiolol had no apparent effects on the action potential or ionic currents of ventricular myocytes, while esmolol shortened action potential duration and demonstrated a negative inotropic effect in a dose related fashion.\textsuperscript{12} This could explain why landiolol has less negative inotropic effect. However, the detailed mechanism is still unknown and further investigation is needed.

The efficacy of other antiarrhythmic drugs is widely recognized, though there are possible adverse side effects such as bradycardia, hypotension or proarrhythmia\textsuperscript{1, 4, 13, 14}. Amiodarone is recognized as one of the most potent drugs for the management of arrhythmias and its efficacy in the management of critical tachyarrhythmia in pediatric patients has been reported\textsuperscript{15, 16}. However, in Japan, intravenous administration of amiodarone was approved in 2007, and landiolol was released a little earlier than amiodarone. We started using landiolol as a first line drug for tachyarrhythmia to preserve hemodynamics before the commercial release of amiodarone and we have seen the effectiveness of this novel drug. Therefore we have no clinical experience
to contrast landiolol with amiodarone in pediatric tachyarrhythmia.

Amiodarone should be used with caution when treating children because of the adverse side effects including a 36% rate of hypotension and a 20% rate of bradycardia. Moreover since the plasma half-life of amiodarone is 14 days, adverse side effects could be prolonged when they appear in critical situation.

In contrast, the ultra-short half-life of landiolol provides the advantage of rapid dose manipulation to maintain stable hemodynamics and this may make landiolol more suitable for emergency medical care.

The recommended loading dose of landiolol based on the company’s instruction is 40 μg / kg / min and the maintenance dose is 10 μg / kg / min. However, we experience one case of bradycardia which required atrial pacing. In addition, based on our experience of using landiolol in adult patients in JL-KNIGHT study, we speculated that the loading dose of 40 μg / kg / min could be too much for pediatric patients. Therefore, we recommend a low starting dose of 3 to 5 μg / kg / min instead of a high loading dose, and the dose should be increased gradually under careful hemodynamic observation with backup pacing.

Limitations
The numbers of cases we have examined are relatively small to have any strong conclusions. Nevertheless this is still the country’s largest experience of this newly developed drug in pediatric population as far as we know. Also our study did not make comparisons of landiolol hydrochloride with other anti-arrhythmia drugs including amiodarone. Further comparative studies with other anti-arrhythmia drugs and more information in a larger series of patients would be necessarily to assess the effectiveness of landiolol for rate and rhythm control in pediatric patients.

Conclusion

Landiolol was efficacious in treating intractable tachyarrhythmia in pediatric patients after cardiac surgery. This study suggests that landiolol may be a promising option for the management of postoperative tachyarrhythmias in pediatric patients.

Acknowledgment

The authors wish to thank Joseph H. Gorman, III, MD, University of Pennsylvania for the language review.
References


11. 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


## Table 1.  Patient characteristic

<table>
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<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Operative procedure</th>
<th>Body weight (kg)</th>
<th>Sex</th>
<th>Age</th>
<th>Bypass time (min)</th>
<th>Cross clamp time (min)</th>
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<td>1</td>
<td>TGA</td>
<td>ASO</td>
<td>3.3</td>
<td>M</td>
<td>10 days</td>
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<td>106</td>
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<td>2</td>
<td>IAA, VSD</td>
<td>Ao repair + ICR</td>
<td>3.4</td>
<td>M</td>
<td>17 days</td>
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<td>71</td>
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<td>3</td>
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<td>ICR</td>
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<td>M</td>
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<td>Extra TCPC</td>
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<td>DKS+BDG</td>
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<td>F</td>
<td>1 year</td>
<td>160</td>
<td>107</td>
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<td>TAPVC</td>
<td>TAPVCrepair</td>
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<td>M</td>
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<td>HLHS</td>
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<td>3.3</td>
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<td>M</td>
<td>5 years</td>
<td>145</td>
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</table>

| Mean | 8.4 | 169.2 | 85.4 |
| SE   | 1.6 | 15.5  | 6.5  |

ASO: Aortic switch operation, BDG: Bidirectional Glenn,
BCPS: Bidirectional cavopulmonary shunt, DILV: Double inlet left ventricle,
DKS: Damus-Kaye-Stansel, DORV: Double outlet right ventricle,
HLHS: Hypoplastic left heart syndrome, HOCM: Hypertrophic obstructive cardiomyopathy,
IAA: Interrupted aortic arch, NW: Norwood operation,
PA: Pulmonary atresia, PS: Pulmonary stenosis,
SV: Single ventricle, TAPVC: Total anomalous pulmonary vein connection,
TCPC: Total cavopulmonary connection, TOF: Tetralogy of Fallot,
TGA: Transposition of great arteries, VSD: Ventricular septal defect,
Table 2. Hemodynamic data of pre and post landiolol hydrochloride administration.

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of arrhythmia</th>
<th>Sinus conversion</th>
<th>Pre sBP (mmHg)</th>
<th>Post sBP (mmHg)</th>
<th>Pre HR (bpm)</th>
<th>Post HR (bpm)</th>
<th>Time to 20% HR reduction (hr)</th>
<th>Time to SR conversion (hr)</th>
<th>Loading dose of landiolol (μg/kg/min)</th>
<th>Maintenance dose of landiolol (μg/kg/min)</th>
<th>dosage of dopamine (γ)</th>
<th>dosage of PDE III inhibitor (γ)</th>
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Mean 82.3 83.7 169.7 127.7 2.3 7.9 11.3 6.8 5.5 0.4
SE    6.6 5.1 11.4 7.5 1.5 2.8 4.0 0.9 1.3 0.1

Figure 1. Heart rate, pre and post landiolol hydrochloride administration in each case. * $p < 0.05$