Effects of Landiolol Hydrochloride on Intractable Tachyarrhythmia After Pediatric Cardiac Surgery

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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.

(255words)

Intractable tachyarrhythmia after pediatric cardiac surgery can quickly lead to hemodynamic instability and requires prompt management [1 2 3]. While β-blockers can be effective in controlling these tachyarrhythmias, a negative inotropic influence sometimes complicates their use [4].

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 [5]. Landiolol has become a common therapeutic option for the management of postoperative tachyarrhythmia in adult patients in Japan [6 7]. 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 [5]. 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 [7]. 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 [8]. 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 [9]. 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 [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. [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 proarrythmia [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 [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 [13]. 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 [8], 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.

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References

1. Dodge-Khatami A, Miller OI, Anderson RH, et al. Surgical substrates of postoperative junctional ectopic tachycardia in congenital heart defects. J Thorac Cardiovasc Surg 2002;123:624-630.

2. Valsangiacomo E, Schmid ER, Schupbach RW, et al. Early postoperative arrhythmias after cardiac operation in children. Ann Thorac Surg 2002;74:792-796.

3. Delaney JW, Moltedo JM, Dziura JD, Kopf GS, Snyder CS. Early postoperative arrhythmias after pediatric cardiac surgery. J Thorac Cardiovasc Surg 2006;131:1296-1300.

4. Dodge-Khatami A, Miller OI, Anderson RH, Gil-Jaurena JM, Goldman AP, de Leval MR. Impact of junctional ectopic tachycardia on postoperative morbidity following repair of congenital heart defects. Eur J Cardiothorac Surg 2002;21:255-259.

5. Atarashi H, Kuruma A, Yashima M, et al. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. Clin Pharmacol Ther 2000;68:143-150.

6. Ito H, Sobue K, So M, et al. Use of landiolol in the perioperative management of supraventricular tachycardia. J Anesth 2006;20:253-254.

7. Sezai A, Minami K, Nakai T, et al. Landiolol hydrochloride for prevention of atrial fibrillation after coronary artery bypass grafting: new evidence from the PASCAL trial. J Thorac Cardiovasc Surg 2011;141:1478-1487.

8. Sakamoto A, Kitakaze M, Takamoto S, Namiki A, Kasanuki H, Hosoda S. Landiolol, an Ultra-Short-Acting beta(1)-Blocker, More Effectively Terminates Atrial Fibrillation Than Diltiazem After Open Heart Surgery. Circ J 2012;76:1097-1101.

9. Adamson PC, Rhodes LA, Saul JP, et al. The pharmacokinetics of esmolol in pediatric subjects with supraventricular arrhythmias. Pediatr Cardiol 2006;27:420-427.

10. Ikeshita K, Nishikawa K, Toriyama S, et al. Landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts. J Anesth 2008;22:361-366.

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

on blood pressure than esmolol. Can J Anaesth 2001;48:985-989.

12. Shibata S, Okamoto Y, Endo S, Ono K. Direct effects of esmolol and landiolol on cardiac function, coronary vasoactivity, and ventricular electrophysiology in guinea-pig hearts. J Pharmacol Sci 2012; 118:255-265.

13. Saul JP, Scott WA, Brown S, et al. Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. Circulation 2005;112:3470-3477.

14. Wong KK, Potts JE, Etheridge SP, Sanatani S. Medications used to manage supraventricular tachycardia in the infant a North American survey. *Pediatr Cardiol.* 2006;27:199-203.

15. Figa FH, Gow RM, Hamilton RM, Freedom RM. Clinical efficacy and safety of intravenous Amiodarone in infants and children. Am J Cardiol 1994;74:573-577.

16. Perry JC, Fenrich AL, Hulse JE, Triedman JK, Friedman RA, Lamberti JJ. Pediatric use of intravenous amiodarone: efficacy and safety in critically ill patients from a multicenter protocol. J Am Coll Cardiol 1996;27:1246-1250.

Table 1. Patient characteristic

Case	Diagnosis	Operative procedure	Body weight (kg)	Sex	Age	Bypass time (min)	Cross clamp time (min)
1	TGA	ASO	3.3	M	10 days	269	106
2	IAA,VSD	Ao repair + ICR	3.4	M	17 days	144	71
3	TOF	ICR	8.4	M	1 year	151	91
4	Asplenia, SV	Extra TCPC	13.7	M	5 years	157	69
5	DILV, CoA	DKS+BDG	7.7	F	1 year	160	107
6	TAPVC	TAPVCrepair	2.8	M	4 days	166	71
7	DORV	DKS	7.0	M	1 year	257	68
8	Asplenia, PA	BCPS	15.2	F	9 years	90	-
9	TGA	Senning	5.2	M	30 days	179	107
10	HLHS	NW	3.3	F	6 days	209	108
11	HOCM	Myectomy	19.2	M	6 years	103	56
12	DILV, PS	Extra TCPC	11.5	M	5 years	145	-
	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,

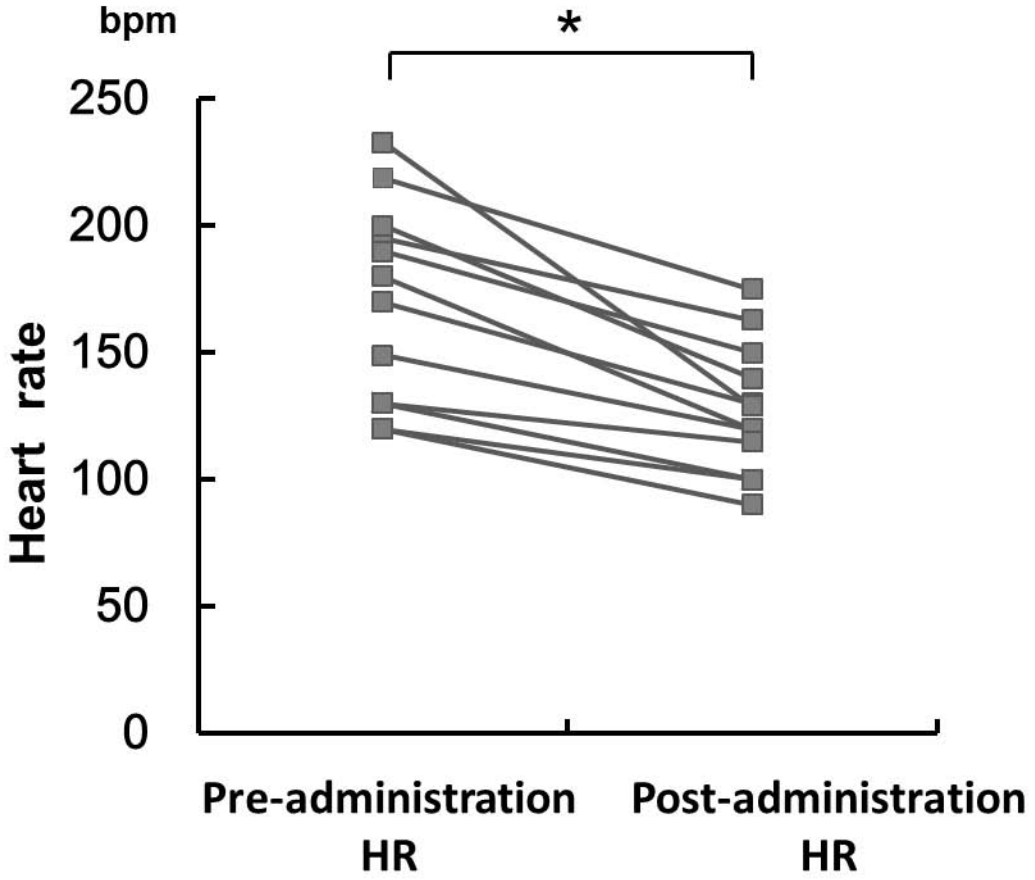
TGA: Transposition of great arteries, VSD: Ventricular septal defect,

Table 2. Hemodynamic data of pre and post landiolol hydrochloride administration.

Case	Type of arrythmia	Sinus conversion	Pre sBP (mmHg)	Post sBP (mmHg)	Pre HR (bpm)	Post HR (bpm)	Time to 20% HR reduction(hr)	Time to SR conversion (hr)	Loadidng dose of landiolol (μg/kg/min)	Maintenance dose of landiolol (μg/kg/min)	dosage of dopamin (γ)	dosage of PDEⅢ inhibitor (γ)
1	JET	yes	48	56	195	163	6	10	40	10	7.5	0.25
2	JET	no	75	72	219	175	1	-	3	8	3	0.5
3	JET	yes	59	70	170	130	2	5	4	8	10	0.5
4	JET	yes	73	72	130	100	1	5	5	10	5	0.5
5	JET	yes	110	120	200	140	2	4	4	8	10	0.75
6	AF	no	74	75	180	120	3	-	3	1	0	0
7	AF	no	112	99	149	120	4	-	5	5	10	0.75
8	af	yes	104	99	120	100	2	5	40	10	9	0.25
9	PSVT	yes	75	85	233	129	2	24	5	7	1	0
10	WPW AVRT	yes	80	75	130	115	2	2	3	3	0	0.25
11	sinus tachy	-	117	101	120	90	1	-	8	8	0	0
12	sinus tachy	-	60	80	190	150	2	-	16	4	10	0.5
	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

af: Atrial fibrillation, AF: Atrial flutter, BP: blood pressure, HR: heart rate, JET: Junctional ectopic tachycardia, PDEⅢinhibitor: phosphodiesteraseⅢinhibitor、PSVT: Paroxysmal supraventricular tachycardia, SR: sinus rhythm, WPW AVRT: Wolff-Parkinson White Syndrome and Atrioventricular reciprocating tachycardia

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


bpm
*
250
200
150
100
50
0
Heart rate
Pre-administration HR
Post-administration HR