Laboratory Investigations

Modifications of the hemodynamic consequences of theophylline intoxication with landiolol in halothane-anesthetized dogs

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Purpose: To examine the effect of landiolol (ONO-1101), a new ultra-short acting, highly selective $beta_1$ blocker, on hemodynamic response to acute theophylline intoxication in anesthetized dogs.

Methods: Thirty-four dogs were studied during halothane anesthesia. Aminophylline (50 $mg \cdot kg^{-1}$ over 20 min followed by infusion at 1.75 $mg \cdot kg^{-1} \cdot hr^{-1}$) was administered as a model of acute theophylline intoxication. Dogs were randomly enrolled into four landiolol groups (0, 1, 10, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to treat tachyarrhythmias. Hemodynamic variables, heart rate (HR), systemic blood pressure (SBP), pulmonary artery pressure, pulmonary artery occlusion pressure, and cardiac output (CO) were measured along with plasma concentrations of theophylline, epinephrine, and norepinephrine.

Results: After 60 min, plasma concentration of theophylline reached 46.6 ± 4.0 (mean ± SD) $\mu g \cdot ml^{-1}$, HR increased from 129 ± 21 to 193 ± 27 bpm ($P < 0.0001$) and CO increased from 1.6 ± 0.5 $l \cdot min^{-1}$ to 2.1 ± 0.4 $l \cdot min^{-1}$ ($P < 0.0001$), whereas SBP decreased from 139 ± 25 to 121 ± 25 mm Hg ($P < 0.0001$), with decreasing systemic vascular resistance. After intoxication, plasma epinephrine concentration increased from 125 ± 112 to 325 ± 239 $pg \cdot ml^{-1}$ ($P < 0.0001$), and norepinephrine concentration from 103 ± 61 to 133 ± 61 $pg \cdot ml^{-1}$ ($P < 0.0011$). Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased HR to pre-intoxication level, whereas HR returned to the intoxication baseline by 30 min after cessation of landiolol infusion.

Conclusions: Landiolol controlled tachyarrhythmias associated with theophylline toxicity. The optimal effective dose of landiolol was 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Objectif : Examiner l'effet du landiolol (ONO-1101), nouveau bloqueur $beta_1$ hypersélectif à action ultrabrève, sur la réponse hémodynamique de l'intoxication aiguë à la théophylline chez des chiens anesthésiés.

Méthode : L'étude a porté sur 34 chiens anesthésiés à l'halothane. L'aminophylline (50 $mg \cdot kg^{-1}$ pendant 20 min, suivi d'une perfusion à 1,75 $mg \cdot kg^{-1} \cdot hr^{-1}$) a été administrée pour provoquer l'intoxication aiguë à la théophylline. Les chiens, répartis au hasard en quatre groupes, ont reçu différentes doses de landiolol (0, 1, 10, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) pour traiter la tachyarythmie. On a mesuré : la fréquence cardiaque (FC), la pression sanguine systémique (PSS), la pression artérielle pulmonaire, la pression artérielle pulmonaire bloquée et le débit cardiaque (DC) de même que les concentrations plasmatiques de théophylline, d'épinéphrine et de norépinéphrine.

Résultats : Après 60 min, la concentration plasmatique de théophylline était de 46,6 ± 4,0 (moyenne ± écart type) $\mu g \cdot ml^{-1}$, la FC avait augmenté de 129 ± 21 à 193 ± 27 bpm ($P < 0,0001$) et le DC était passée de 1,6 ± 0,5 $l \cdot min^{-1}$ à 2,1 ± 0,4 $l \cdot min^{-1}$ ($P < 0,0001$), tandis que la PSG avait baissé de 139 ± 25 à 121 ± 25 mm Hg ($P < 0,0001$) et que la résistance vasculaire générale diminuait. Après l'intoxication, la concentration plasmatique d'épinéphrine a augmenté de 125 ± 112 à 325 ± 239 $pg \cdot ml^{-1}$ ($P < 0,0001$), et la concentration de norépinéphrine est passée de 103 ± 61 à 133 ± 61 $pg \cdot ml^{-1}$ ($P < 0,0011$). Les 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ de landiolol ont fait baisser la FC au niveau observé avant l'intoxication, mais la FC a retrouvé la valeur du début de l'intoxication 30 min après l'arrêt de la perfusion de landiolol.

Conclusion : Le landiolol a contrôlé la tachyarythmie associée à une toxicité induite par la théophylline. La dose d'efficacité optimale a été de 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

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BETA-ADRENERGIC receptor blockers have been extensively used in the treatment of hypertension, effort angina, and cardiac arrhythmias.[1,2] Various types of beta blocker have been developed, but their use has been limited because of undesirable properties, such as bronchoconstriction, prolonged hypotension, and myocardial depression, which is attributed to their long duration of action. Zaroslinski and co workers[3] demonstrated that esmolol, an ultra-short acting, highly cardioselective beta-adrenergic receptor antagonist is effective in the treatment of critically ill patients. Several investigators have also documented that it controls hemodynamic changes in clinical situations.[4–6] Another ultra-short acting beta blocker, landiolol (ONO-1101) {(-)-[(S)-2,2-dimethyl-1, 3-dioxolan- 4-yl] methyl 3-[4-[(S)-2-hydroxy-3-(2-morpholino carbonylamino) ethyl-amino] propoxy] phenylpropionate monohydrochloride}, has more potent cardiac properties than esmolol,[7] and has been developed for application in the emergency treatment of tachyarrhythmias in animals.[7–9] Theophylline toxicity induces severe tachyarrhythmias in humans[10–12] and in an animal model.[13] The purpose of this study was to examine the effect of landiolol on hemodynamics during acute theophylline intoxication in halothane-anesthetized dogs.

Methods

Animal preparation

The study protocol was approved by our institutional animal care committee. Thirty-four adult mongrel dogs of either sex and weighing 9.5-13.5 kg were anesthetized with 25 $mg \cdot kg^{-1}$ pentobarbital *iv*. The trachea of each dog was intubated with a cuffed endotracheal tube, and the lungs were mechanically ventilated (Harvard Model 613® Apparatus Company, Chicago, USA) at tidal volume of 15 $ml \cdot kg^{-1}$ at a respiratory rate sufficient to maintain normoventilation. End-tidal CO_2 tension was continuously monitored. Anesthesia was maintained with 1.2 MAC (1.0% at end-tidal concentration) halothane in oxygen. These concentrations were monitored with a respiratory/anesthetic gas analyser (Capnomac Ultima®, Datex instrumentarium, Helsinki, Finland) calibrated with a standard gas. The femoral artery and vein were cannulated for arterial blood pressure monitoring, blood sampling, and drug and fluid administration. Drug infusions were delivered via motor driven syringe pumps (Termo Model STC-523®, Tokyo, Japan). The contralateral femoral vein was cannulated with a pulmonary artery catheter (Swan-Ganz Catheter®, Baxter Healthcare Corporation Edwards Critical-Care Division, Santa Ana, CA, USA) to measure pulmonary artery pressure, pulmonary artery occlusion pressure, central venous pressure, cardiac output and blood temperature (Cardiac Output Computer 7350®, Arrow, Reading, PA, USA). Lead II of the ECG was monitored continuously and recorded (Polygraph 7747 Amplifier Case®, San-ei, Tokyo, Japan). Additional monitoring included arterial blood gas analysis, electrolyte and hemoglobin concentrations (Ciba Coring 288 Blood Gas System®, Ciba Corning Diagnostics Corp. Medfield, MA, USA). Maintenance fluid (Ringer's lactate solution) was administered at a rate of 10 $ml \cdot kg^{-1} \cdot hr^{-1}$. Metabolic acidosis (base excess < -10.0) was corrected with sodium bicarbonate as required. Serum potassium concentration was maintained between 3.5-4.5 $mEq \cdot l^{-1}$ by infusing KCl as required. Arterial pH, PO_2, and serum sodium concentration were maintained within the range of 7.35-7.45, 100-200 mm Hg, 135-145 $mEq \cdot l^{-1}$, respectively. During the study, blood temperature was maintained between 36.5-38.5°C using a hot-water pad. After at least 90 min of stabilization of halothane-oxygen anesthesia, measurements of all hemodynamic variables including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary artery occlusion pressure (PAOP), cardiac output (CO) and plasma concentration of catecholamines (epinephrine and norepinephrine) were taken to define the pre-intoxication baseline. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were derived according to the following equation: SVR = {(MBP - CVP) × 80}/CO, and PVR = {(MPAP - PAOP) ×80}/CO.

Theophylline intoxication

The model of acute theophylline toxicity was made using the method described by Gaar *et al.*[14] Aminophylline was administered as an *iv* infusion at a dose of 50 $mg \cdot kg^{-1}$ body weight over 20 min. This was followed by continuously administering 1.75 $mg \cdot kg^{-1} \cdot hr^{-1}$ aminophylline throughout the experiment. This dose design was based on the knowledge of the volume of distribution and the elimination characteristics, to achieve serum theophylline concentration >35 $\mu g \cdot ml^{-1}$, which were considered to be in the toxic range. Hemodynamic variables were measured every 10 min until 60 min after the beginning of aminophylline administration. Blood sampling for measuring of plasma concentrations of catecholamines and theophylline was performed at least 60 min after theophylline-intoxication.

Landiolol infusion during theophylline intoxication

At least 60 min after intoxication of theophylline, stabilization of the intoxicated state was defined as HR and SBP that remained within 10% variation over five minutes. After measurements of hemodynamic baseline variables, dogs were assigned randomly to one of four landiolol groups: 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ group (n = 9), 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ group (n = 9), 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ group (n = 8), and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ group (n = 8). Landiolol was administered for 30 min. Hemodynamic variables were measured before, 15, and 30 min after landiolol administration. Hemodynamic variables were also measured 15 and 30 min after landiolol cessation. Blood samples for measuring the plasma concentration of catecholamines and theophylline were obtained at the end of infusion of landiolol. Then, the samples for measuring catecholamine concentration were withdrawn into plastic tubes containing EDTA-2Na. These were then centrifuged at 3000 rpm for 10 min at 2°C to separate the plasma. Epinephrine and norepinephrine in deproteinized plasma were determined by an automated double-column HPLC system (Model CA825®, Tosho Co., Ltd., Tokyo, Japan). This assay system is based on the trihydroxyindole reaction, and has a limit of sensitivity of 5 $pg \cdot ml^{-1}$ for epinephrine and inter and intra-assay variations are less than 3%. Blood samples for measuring the plasma concentration of theophylline were withdrawn into plastic tubes and were then centrifuged at 3000 rpm for 10 min at 2°C to separate the plasma. Plasma concentrations were measured by enzyme multiplied immunoassay technique (Model 7170®, Hitachi Co., Ltd., Tokyo, Japan).

The data were expressed as mean ± SD. Statistical analysis was performed using a commercially available software package (StatView® Ver.4.5, Abacus Concepts, Inc., Berkeley, CA, USA). Hemodynamic parameters, catecholamines and theophylline concentrations, at different doses of landiolol were analyzed using analysis of variance (ANOVA) with Bonferroni's correction. The data of each group were analyzed using paired t test. P value of < 0.05 was considered significant.

Results

Theophylline intoxication

The hemodynamic changes after theophylline infusion are shown in Table I. Post-intoxication values obtained 60 min after administration of aminophylline, showed increases in HR and CO, and decreases in SBP, DBP, MBP, SVR, and PVR from baseline values. These hemodynamic changes continued during theophylline infusion (Figure 1). After theophylline intoxication, plasma epinephrine concentrations increased from 125 ± 112 $pg \cdot ml^{-1}$ at baseline to 325 ± 239 $pg \cdot ml^{-1}$, and plasma norepinephrine concentrations increased from 103 ± 61 to 133 ± 61 $pg \cdot ml^{-1}$ (Table I). Plasma theophylline concentration reached >35 $\mu g \cdot ml^{-1}$ in all animals and the mean theophylline concentration after theophylline intoxication was 66.8 ± 12.8 $\mu g \cdot ml^{-1}$ at 30 min after theophylline infusion, and 46.7 ± 4.0 $\mu g \cdot ml^{-1}$ at 60 min after theophylline infusion. Dysrhythmias associated with theophylline intoxication were observed in eight of 34 (23%) animals.

TABLE I Hemodynamic changes after theophylline intoxication

	Pre-intoxication	*Post-intoxication*
HR (bpm)	129 ± 21	193 ± 27*
SBP (mmHg)	139 ± 25	121 ± 25*
DBP (mmHg)	98 ± 16	75 ± 15*
MBP (mmHg)	114 ± 18	94 ± 17*
CVP (mmHg)	1.7 ± 0.9	1.9 ± 0.7
MPAP (mmHg)	13 ± 4	13 ± 3
PAOP (mmHg)	5 ± 2	6 ± 2
Cardiac output ($l \cdot min^{-1}$)	1.6 ± 0.5	2.1 ± 0.4*
SVR ($dyne \cdot sec \cdot cm^{-5}$)	5809 ± 1417	3598 ± 779*
PVR ($dyne \cdot sec \cdot cm^{-5}$)	411 ± 225	276 ± 94*
Plasma epinephrine concentration ($pg \cdot ml^{-1}$)	125 ± 112	325 ± 239*
Plasma norepinephrine concentration ($pg \cdot ml^{-1}$)	103 ± 61	133 ± 61*

Values are mean ± SD. Post-intoxication values were obtained at 60 min after intoxication.

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, CVP = central venous pressure, MPAP = mean pulmonary artery pressure, PAOP = pulmonary artery occlusion pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance.

*$P < 0.05$ *vs* pre-intoxication values.

Landiolol infusion during theophylline intoxication

The hemodynamic changes after administration and cessation of landiolol are shown in Table II. Decreases in HR were observed in the groups that received ≥ 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol (Figure 2). These decreased HR values during landiolol were not different from pre-intoxication values. There were no differences among the groups in terms of SBP, DBP, MBP, CVP, PAP, PAOP, CO, SVR and PVR after landiolol administration. However, decreases in SBP were observed compared with intoxication baseline (immediately before administration of landiolol) in the group receiving 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol. Decreases in SBP, DBP, MBP and MPAP were observed compared with baseline after theophylline in the group receiving 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol. On the other hand, no differences in CO were observed compared with

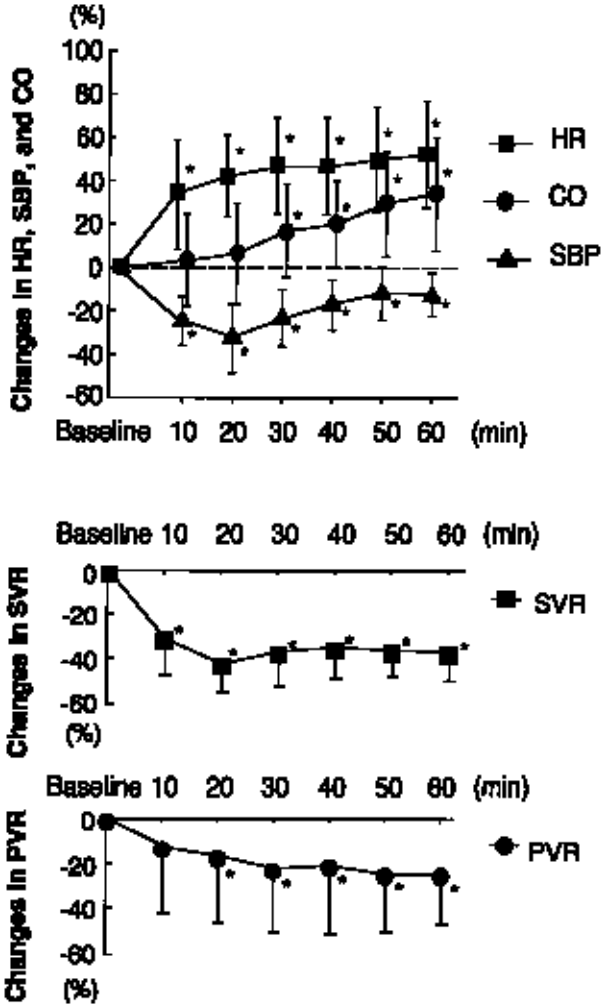

FIGURE 1
Upper panel: Changes in heart rate (HR), systolic blood pressure (SBP), and cardiac output (CO) after *iv* injection of aminophylline in halothane-anesthetized dogs. Values are mean ± SD. * $P < 0.05$ *vs* baseline (preinjection) values.
Middle panel:Changes in systemic vascular resistance (SVP) after *iv* injection of aminophylline in halothane-anesthetized dogs. Values are mean ± SD. * $P < 0.05$ *vs* baseline (preinjection) values.
Lower panel:Changes in pulmonary vascular resistance (PVR) after *iv* injection of aminophylline in halothane-anesthetized dogs. Values are mean ± SD. * $P < 0.05$ *vs* baseline (preinjection) values.

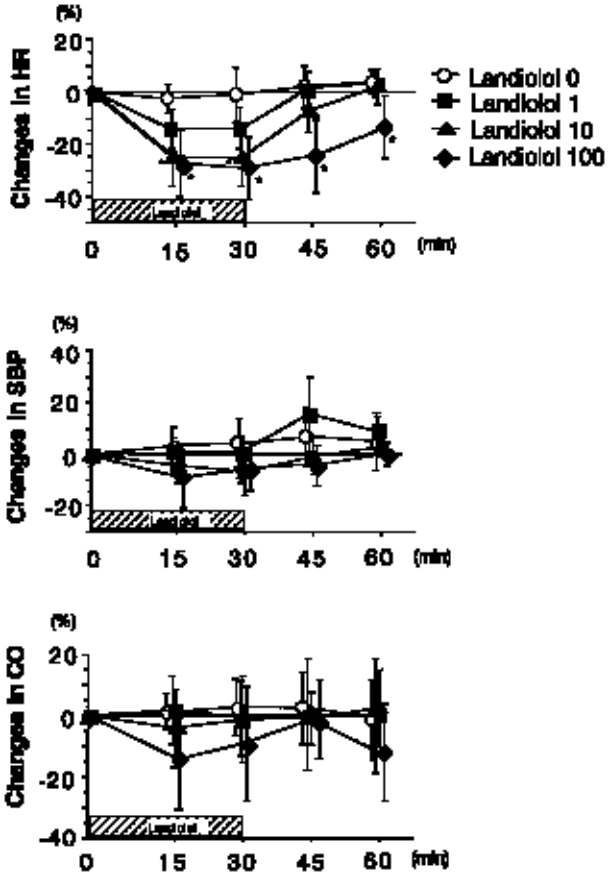

FIGURE 2 Changes in heart rate (HR, upper panel), systolic blood pressure (SBP, middle panel), and cardiac output (CO, lower panel) after *iv* injection of landiolol during theophylline intoxication in halothane- anesthetized dogs. Infusions of landiolol were continued for 30 min. Values are mean ± SD. * $P < 0.05$ *vs* landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to post-hoc comparison.

intoxication baseline in the group receiving 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol. Treatments with landiolol did not change SVR, PVR, CVP, or PAOP in any group (Table II). In the control group, increases in HR, PAP, and PAOP were observed compared with intoxication baseline during observation.

After cessation of landiolol, HR returns to the intoxication baseline value by 30 min with the exception of the group receiving 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol. (Figure 2) However, in the group receiving 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol, HR returned to the intoxication baseline value within 60 min after cessation of landiolol.

Plasma epinephrine and norepinephrine concentrations were not affected by administration of landiolol (Table III). Plasma theophylline concentrations of all subjects remained within the toxic range (>35 $\mu g \cdot ml^{-1}$) through the study, and there were no differences among the groups after landiolol administration (Table IV).

TABLE II Variables after treatment and cessation of landiolol

		Intoxication Baseline	*Landiolol*[a]	*After cessation*[b]
Heart rate (bpm)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	192 ± 12	190 ± 23	199 ± 14*
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	203 ± 17	177 ± 19*	209 ± 19
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	182 ± 28	134 ± 18* †	185 ± 27
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	188 ± 31	132 ± 19*†	162 ± 26*†
SIBP (mmHg)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	146 ± 45	153 ± 47	154 ± 47
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	136 ± 28	139 ± 28	147 ± 32*
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	122 ± 22	114 ± 22*	126 ± 23
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	128 ± 21	115 ± 23*	125 ± 24
DBP (mmHg)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	93 ± 16	95 ± 14	96 ± 14
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	85 ± 21	90 ± 22	86 ± 21
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	78 ± 18	74 ± 20	79 ± 16
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	79 ± 15	73 ± 17*	80 ± 17
MBP (mmHg)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	113 ± 22	115 ± 21	117 ± 21
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	104 ± 22	107 ± 22	108 ± 22*
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	94 ± 19	90 ± 20	96 ± 17
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	97 ± 18	90 ± 19*	97 ± 17
CVP (mmHg)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	1.6 ± 1.3	1.6 ± 1.2	1.4 ± 1.5
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	2.1 ± 1.7	2.0 ± 1.1	1.2 ± 1.2
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	2.1 ± 0.6	2.3 ± 1.2	3.0 ± 1.7
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	2.5 ± 1.5	3.0 ± 2.3	2.5 ± 0.9
MPAP (mmHg)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	16 ± 6	17 ± 7*	17 ± 7
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	20 ± 7	19 ± 6	18 ± 5
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	17 ± 9	14 ± 6	16 ± 6
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	16 ± 5	14 ± 3*	17 ± 8
PAOP (mmHg)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	7 ± 4	10 ± 4*	9 ± 4
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	10 ± 5	11 ± 5	7 ± 4
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	11 ± 8	7 ± 5	10 ± 6
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	8 ± 5	6 ± 2	8 ± 6
CO ($l \cdot min^{-1}$)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	2.0 ± 0.7	2.0 ± 0.7	1.9 ± 0.5
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	1.7 ± 0.5	1.7 ± 0.6	1.8 ± 0.7
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	1.9 ± 0.6	1.6 ± 0.4	1.7 ± 0.7
SVR ($dyne \cdot sec \cdot cm^{-5}$)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	4791 ± 933	4788 ± 687	5034 ± 757
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	4449 ± 1589	4619 ± 1455	4612 ± 1195
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	4555 ± 1466	4418 ± 1463	4537 ± 1430
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	4254 ± 1222	4454 ± 1015	4961 ± 1704
PVR ($dyne \cdot sec \cdot cm^{-5}$)				
Landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	359 ± 110	315 ± 113	355 ± 130
Landiolol 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 9)	405 ± 155	377 ± 188	463 ± 163
Landiolol 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	294 ± 128	366 ± 199	302 ± 109
Landiolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$	(n = 8)	360 ± 114	413 ± 122	453 ± 191

Values are mean ± SD. SBP = systolic blood pressure, DBP diastolic blood pressure, MBP = mean blood pressure, CVP central venous pressure, MPAP = mean pulmonary artery pressure, PAOP = pulmonary artery occlusion pressure, CO Cardiac output, SVR systemic vascular resistance, PVR pulmonary vascular resistance.

[a]Obtained at 30 min after landiolol infusion; [b]Obtained at 30 min after cessation of landiolol infusion.

* $P < 0.05$ *vs* intoxication baseline values. † $P < 0.05$ *vs* landiolol 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

TABLE III Plasma concentrations of epinephrine, and norepinephrine during theophylline intoxication

		Baseline[a]	*Intoxication*[b]	*Landiolol*[c]
Epinephrine concentration (pg·ml⁻¹)				
Landiolol 0 μg·kg⁻¹·min⁻¹	(n = 9)	131 ± 110	232 ± 80*	161 ± 67
Landiolol 1 μg·kg⁻¹·min⁻¹	(n = 9)	163 ± 223	430 ± 555	315 ± 387
Landiolol 10 μg·kg⁻¹·min⁻¹	(n = 8)	140 ± 123	443 ± 283*	333 ± 262
Landiolol 100 μg·kg⁻¹·min⁻¹	(n = 8)	121 ± 123	385 ± 300*	306 ± 248
Norepinephrine concentration (pg· ml⁻¹)				
Landiolol 0 μg·kg⁻¹·min⁻¹	(n = 9)	130 ± 73	125 ± 53	206 ± 93*
Landiolol 1 μg·kg⁻¹·min⁻¹	(n = 9)	120 ± 76	189 ± 50*	363 ± 61*
Landiolol 10 μg·kg⁻¹·min⁻¹	(n = 8)	89 ± 52	135 ± 76	273 ± 212*
Landiolol 100 μg·kg⁻¹·min⁻¹	(n = 8)	86 ± 49	138 ± 70	289 ± 206

Values are mean ± SD.

[a]Obtained immediately before intoxication of theophylline. [b]Obtained after intoxication of theophylline. [c]Obtained after treatment of landiolol.

*$P < 0.05$ *vs* baseline value.

TABLE IV Plasma concentrations of theophylline during theophylline intoxication

Landiolol dose (μg·kg⁻¹·min⁻¹)		*Intoxication baseline*[a]	*Landiolol*[b]
Theophylline concentration (μg·ml⁻¹)			
Landiolol 0 μg·kg⁻¹·min⁻¹	(n = 9)	48 ± 2	43 ± 3
Landiolol 1 μg·kg⁻¹·min⁻¹	(n = 9)	46 ± 5	42 ± 4
Landiolol 10 μg·kg⁻¹·min⁻¹	(n = 8)	46 ± 5	43 ± 4
Landiolol 100 μg·kg⁻¹·min⁻¹	(n = 8)	47 ± 5	42 ± 4

Values are mean ± SD. [a]Obtained immediately before infusion of landiolol. [b]Obtained 30 min after infusion of landiolol.

*$P < 0.05$ *vs* baseline value.

Dysrhythmia disappeared after landiolol administration (1 μg·kg^{-1}·min^{-1}) in five of eight dogs. In the remaining three dogs without landiolol treatment, dysrhythmias lasted throughout the study.

Discussion

The findings of the present study are as follows: first, administering aminophylline (50 mg·kg^{-1} loading dose plus 1.75 mg·kg^{-1}·hr^{-1} maintenance dose) induced acute cardiovascular theophylline intoxication: second, administrating 10 μg·kg^{-1}·min^{-1} landiolol during theophylline intoxication decreased HR to pre-intoxication level.

As previously described by Gaar *et al.*,[14] the plasma theophylline concentrations were >35 μg·ml^{-1} for five hours during intoxication. In this study, plasma theophylline concentrations achieved 46.7 ± 4.0 (mean SD) μg·ml^{-1} at the time of commencing landiolol infusion and were maintained above the toxic level (>35 μg·ml^{-1}) in all animals.

A characteristic progression of symptoms in theophylline intoxication has been described.[11,13] Initial cardiovascular signs and symptoms include mild tachycardia and slight hypertension. In the most severe intoxications, severe tachycardia, cardiac arrhythmia, hypotension, and peripheral vascular collapse may occur. In this study, we found severe tachycardia, hypotension, decreases in SVR and PVR, and an increase in CO during infusion. These hemodynamic changes associated theophylline agree with the report of Kearney *et al.*[13] Tachycardia during theophylline intoxication occurs by a direct effect of theophylline on the sinus node, an increase in sympathetic nervous system activity, or an increase in catecholamines.[10,13] In this study, plasma concentrations of catecholamines increased from baseline values after administration of aminophylline. The findings are consistent with reports that theophylline increased circulating levels of catecholamines.[10,11,13] The increases in plasma catecholamine concentrations correlated with the dose-related increases in HR observed during their study, supporting the hypothesis that the cardiovascular effects of theophylline may be mediated in part by the beta-adrenergic system.

Most adverse effects of beta blocker use are related to interference with beta$_2$ mediated function including

bronchodilation and vasodilation.[1,2] Thus, to avoid these disadvantages, selective $beta_1$ blockade is required. Landiolol has been developed as an ultrashort acting beta blocker, and has been reported to be nine times more potent than esmolol.[7] In addition to these properties, landiolol has highly selective $beta_1$-adrenoceptor activity ($beta_1/beta_2$-receptor activity ($ß_1/ß_2$) = 255) which studied *in vitro* with guinea pig right atria and trachea strips.[7] Its $beta_1$ selectivity is greater than that of other beta blockers, such as esmolol ($ß_1/ß_2$ = 33) and propranolol ($ß_1/ß_2$ = 0.68).[7] Thus, the high cardioselectivity of landiolol may produce beneficial effects in some patients with bronchial asthma.

$Beta_2$ adrenergic receptors exist on vascular smooth muscle and exert a vasodilating effect. Propranolol, a non- selective beta adrenergic receptor antagonist, reverses the effects of theophylline-induced hypotension, because of the increase in SVR associated with its $beta_2$-blocking effects.[13] By contrast, landiolol, even in the highest dose (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$), did not affect the decrease in SVR associated with theophylline in this study. A lack of effect of landiolol on SVR was demonstrated previously in pentobarbital anesthetized dogs even after 3000 $\mu g \cdot kg^{-1} \cdot min^{-1}$ administration.[15]

Landiolol did not decrease plasma concentrations of norepinephrine in this study. This is in agreement with finding that esmolol, a selective $beta_1$ blocker, did not affect plasma concentrations of norepinephrine.[14] These results suggest that $beta_1$ does not mediate facilitation of norepinephrine from sympathetic nerve terminal. Dahlof *et al.*[16] demonstrated that selective $beta_1$ blocker does not decrease stimulation-evoked norepinephrine overflow, compared with control experiments. They concluded that norepinephrine release could be enhanced by activation of prejunctonal $beta_2$ adrenoceptors *in vivo*.[16]

We found that landiolol reversed the tachycardia induced by theophylline in a dose dependent manner. Consequently, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol is considered to be the optimal effective dose for suppressing an increase in HR during theophylline intoxication. On the other hand, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol did not affect CO compared with intoxication baseline. Thus, landiolol attenuated the positive chronotropic effect of theophylline without blocking the positive inotropic effect.

Dysrhythmias were observed in eight of 34 (23%) halothane-anesthetized dogs during intoxication of theophylline in this study. However, Gaar *et al.*[14] showed no dysrhythmia associated theophylline in alpha chloralose-anesthetized dogs. This difference is considered to be the use of anesthetics, especially halothane. We have previously demonstrated that epinephrine causes dysrhythmias in halothane-anesthetized dogs, and that 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol prevents such dysrhythmias.[17] In this study, the dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ landiolol controlled dysrhythmias associated with theophylline intoxication.

In conclusion, landiolol controlled tachyarrhythmias during theophylline intoxication. The optimal effective dose of landiolol, which decreases HR during intoxication, is determined 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

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