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Effect of landiolol hydrochloride on suxamethonium-induced neuromuscular block

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Abstract
Purpose. The aim of this study was to examine the effect of landiolol hydrochloride, an ultrashort-acting β_1-blocker, on suxamethonium-induced neuromuscular block.
Methods. Thirty patients were randomly allocated to receive a loading dose of landiolol, 0.125 $mg \cdot kg^{-1} \cdot min^{-1}$ for 1 min, followed by an infusion at 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$, or placebo. Twenty minutes after the infusion of landiolol or placebo, suxamethonium 1 $mg \cdot kg^{-1}$ was administered during propofol-fentanyl-nitrous oxide anesthesia. Neuromuscular block was monitored by train-of-four (TOF) responses of the adductor pollicis muscle, applying acceleromyographic stimuli to the ulnar nerve.
Results. The onset of neuromuscular block did not differ between the groups. The time from administration of suxamethonium to spontaneous recovery to the first twitch of TOF (T1) of control was significantly longer in the landiolol group (mean [SD]; 12.2 [2.5] min), when compared with the control group (9.8 [2.6] min). However, the TOF ratios measured when the T1 had spontaneously recovered to 10%, 25%, 50%, 75%, 90%, and 100% of control was comparable between the groups.
Conclusion. Landiolol delayed recovery from suxamethonium-induced paralysis. However, the interaction between the drugs seemed to be small in the clinical setting.

Key words Landiolol · β-blocker · Acceleromyography · Neuromuscular blockade · Suxamethonium

Introduction

It has recently been recognized that β-blockers can reduce the risk of perioperative adverse cardiac events [1,2]. It is particularly important to prevent tachycardia for patients with coronary artery disease. In clinical anesthesia, noxious cardiovascular events are frequently observed during laryngoscopy and tracheal intubation. Therefore, it may be reasonable that β-blockers are used to prevent tachycardia and hypertension during the induction of anesthesia. In fact, the usefulness of propranolol [3] and esmolol [4,5] for perioperative cardiovascular stability has been shown in the literature. Also, information that landiolol hydrochloride, an ultrashort-acting β_1-selective blocker, can effectively attenuate cardiovascular responses to laryngoscopy and tracheal intubation is accumulating [6–8]. The short elimination half-life (4 min) of landiolol is attributed to its rapid hydrolysis by pseudocholinesterase in the plasma [9]. Suxamethonium, which is used for tracheal intubation, is also metabolized by pseudocholinesterase [10]. It was therefore anticipated that, to some extent, there might be an influence of co-administration of landiolol on the metabolism of suxamethonium. The aim of this study was to examine the effect of landiolol on suxamethonium-induced neuromuscular block.

Patients and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 30 adult female patients consented to participate in this study. The patients were American Society of Anesthesiologists physical status I or II, 34–60 years of age, and undergoing elective gynecological surgery. None of the patients had neuromuscular, hepatic, or renal disorders, and none were taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index was 25 or greater or less than 18.5 were excluded from the study.

No patients were premedicated. On arrival at the operating room, all patients were monitored with ECG, noninvasive blood pressure, and pulse oximetry. An i.v. infusion of acetated Ringer's solution 8–10 $ml \cdot kg^{-1} \cdot h^{-1}$ was started via a cannula in the right forearm. Patients were randomly allocated to receive a loading dose of

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Table 1. Patient characteristics

	Age (years)	Weight (kg)	Height (cm)
Control group	42.7 (5.2) [34–49]	53.9 (3.3) [47–60]	158.3 (4.5) [149–164]
Landiolol group	46.7 (7.7) [36–60]	53.7 (5.6) [46–64]	154.7 (4.3) [147–161]

Data values are presented as means (SD) [range]. No significant differences were seen between the groups

landiolol, 0.125 mg·kg^{-1}·min^{-1} for 1 min, followed by an infusion at 0.04 mg·kg^{-1}·min^{-1}, or followed by placebo (physiological saline solution). Five minutes after the infusion, anesthesia was induced with fentanyl 2 μg·kg^{-1} and propofol 2.5 mg·kg^{-1} i.v., while the patients received 100% oxygen through an anesthesia facemask. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anesthesia was maintained with nitrous oxide 67% in oxygen and a propofol infusion of 3–4 mg·kg^{-1}·h^{-1}. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa, using a Multigas Unit AG-920R (Nihon Kohden, Tokyo, Japan). Rectal temperature was monitored using Mon-a-Therm (Mallinckrodt, Anesthesia Products, St. Louis, MO, USA) and patients' temperature was maintained at more than 36°C using a warming mattress and blanket (Thermacare and Medi-Therm II; Gaymer Industries, New York, NY, USA) and warmed i.v. fluids. Skin temperature over the thenar muscle was recorded and kept at more than 32°C.

After a stable depth of anesthesia had been obtained, the ulnar nerve was stimulated at the wrist with square-wave, automatically detected supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) mode at 2 Hz every 15 s, and contraction of the ipsilateral adductor pollicis muscle was measured using acceleromyography (TOF-Watch; Organon, Dublin, Ireland). After the control TOF stimuli were administered for at least 20 min, all patients received suxamethonium 1 mg kg^{-1} i.v. Fasciculations were graded by a blinded observer using a four-point scale: 0, no visible fasciculations; 1, very fine fingertip or facial muscle movements; 2, minor fasciculations on the trunk and extremities; 3, vigorous fasciculations on the trunk and extremities. The following variables were measured: lag time (s) from the time of bolus injection of suxamethonium to the beginning of depression of the first twitch of TOF (T1); onset time (s) from the injection of suxamethonium to maximum depression of T1; time (min) from the injection of suxamethonium to the spontaneous recovery of T1 to 10%, 25%, 50%, 75%, 90%, and 100% of control; and TOF ratios that were measured when the T1 spontaneously recovered to 10%, 25%, 50%, 75%, 90%, and 100% of control.

Data values are presented as means (SD) [range]. Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student's *t*-test was used for comparisons between two groups. A P value of less than 0.05 was considered statistically significant.

Table 2. Graded severity of fasciculations

	0	1	2	3
Control group	0	0	4	11
Landiolol group	0	1	3	11

Data values are presented as patient numbers. No significant differences were seen between the groups

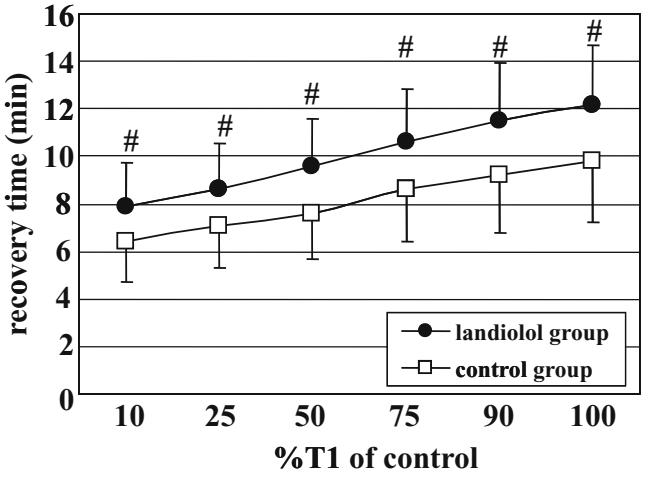

Fig. 1. Comparison of recovery times of the first twitch of TOF (T1). $^{\#}P < 0.05$ compared to the measurements of the control group

Results

Patient characteristics (Table 1), the graded severity of fasciculations (Table 2), and the lag and onset times (Table 3) did not differ between the two groups. The durations of time following suxamethonium injection to the spontaneous recovery of T1 to 10%, 25%, 50%, 75%, 90%, and 100% of control were significantly longer in the landiolol group than those in the control group ($P < 0.05$; Fig. 1). However, the averaged TOF ratios measured when the T1 spontaneously recovered to 10%, 25%, 50%, 75%, 90%, and 100% of control did

Table 3. Lag and onset time following suxamethonium administration

	Maximum block (%)	Lag (s)	Onset (s)
Control group	100 (0)	36.4 (9.7) [30–60]	61.1 (7.1) [45–75]
Landiolol group	100 (0)	38.6 (9.7) [30–60]	63.2 (10.5) [45–75]

Data values are presented as means (SD) [range]. No significant differences were seen between the groups

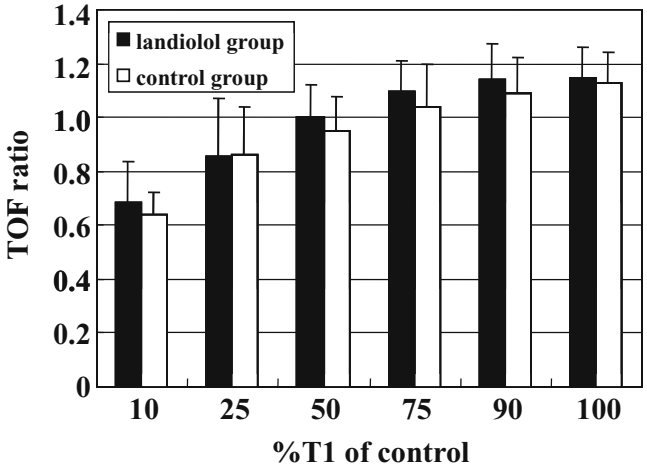

Fig. 2. Comparative train-of-four (*TOF*) ratios observed at the same %T1 of control. No significant differences were seen between the groups

not differ between the groups (Fig. 2). Following the suxamethonium injection, the heart rate increased significantly, from 62.0 (SD, 7.2) to 71.3 (SD, 10.1) bpm in the control group ($P < 0.01$), while no increase was seen in the landiolol-treated group (57.1 [SD, 5.5] vs 58.6 [SD, 5.6] bpm).

Discussion

The present study showed that landiolol significantly delayed recovery from suxamethonium-induced paralysis. Thus far, the potentiating effect of β-blockers on suxamethonium-induced neuromuscular block has been investigated using propranolol in animal studies [11–13]. However, we revealed an interaction between landiolol, a relatively new β_1-selective blocker, and suxamethonium in this human study.

The underlying mechanism has not fully been elucidated. Both landiolol [14] and suxamethonium [10] are hydrolyzed by pseudocholinesterase in plasma and therefore are speculated to compete against each other for the enzyme. Hence, their duration of action may be prolonged. Furthermore, the increased release of catecholamines from α-adrenergic nerve terminals occurring subsequent to β-blockade leads to more acetylcholine being released from the motor nerve endings [15,16]. The increased acetylcholine may have a synergistic effect on suxamethonium-induced block. These speculations may be supported by a similar finding [17] that esmolol, another ultrashort-acting β-blocker that is metabolized by plasma pseudocholinesterase, also delayed recovery from suxamethonium-induced neuromuscular block. Meanwhile, it is well known that propranolol, a classical representative of β-receptor antagonists, intensifies suxamethonium-induced neuromuscular block via its local anesthetic action [11–13]. However, it is unlikely that the local anesthetic action of landiolol would have delayed the recovery of T1 in the present study. Basically, local anesthetic agents at clinical concentrations tend to inhibit acetylcholine release from motor nerve terminals [18]. In clinical settings, the presynaptic inhibition of local anesthetics can decrease the intensity of fasciculation and the rate of postoperative myalgia induced by suxamethonium [19]. In addition, neuromuscular monitoring has revealed that local anesthetic action is easily seen in the increased TOF fade expressing a presynaptic event, compared to the T1 depression of the postsynaptic event [20]. Therefore, our finding of no differences observed between the landiolol-treated group and the control group in the severities of fasciculation and the TOF ratios measured at the same levels of T1 recovery clearly supports the idea that landiolol did not exert local anesthetic action in this study. Actually, no local anesthetic effect was noted even at a high concentration of landiolol in a general pharmacological study using animals [21]. The decreased cardiac output induced by landiolol may slow the rate of redistribution of suxamethonium from the neuromuscular junction into the blood vessels and, hence, delay the recovery from paralysis. However, the onset of action of suxamethonium would certainly be affected by decreased cardiac output and blood flow to the muscle. It was reported that increased cardiac output in patients pretreated with ephedrine could shorten the onset of rocuronium-induced neuromuscular block, while, in contrast, decreased cardiac output following esmolol delayed the onset of this block [22]. In patients with normal cardiac function, landiolol produces a significant decrease in heart rate, but does not decrease cardiac output by a compensatory increase in stroke volume [23]. It is therefore reasonable that, in the present study, the onset of the suxamethonium-induced

neuromuscular block was not altered by landiolol and the delayed recovery from the suxamethonium-induced block was not due to decreased cardiac output.

Suxamethonium increases heart rate considerably via sympathetic stimulation. A marked increase in a patient's plasma concentration of norepinephrine was seen following suxamethonium [24]. We therefore anticipated, in the present study, that landiolol would suppress the increase in plasma norepinephrine level and, hence, prevent the heart rate from increasing after an injection of suxamethonium. As expected, suxamethonium significantly increased the heart rate, by about 10 bpm, in the control group, while no increase was seen in the landiolol-treated group.

In conclusion, landiolol delays recovery from suxamethonium-induced neuromuscular block; however, the time-lag is not clinically significant. Furthermore, landiolol effectively suppresses tachycardia following the administration of suxamethonium. Thus, the combination of landiolol and suxamethonium can be used safely during the induction of anesthesia.

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