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SHORT COMMUNICATION

Metoclopramide does not prolong duration of action of landiolol attenuating the hemodynamic response to induction of anesthesia and tracheal intubation

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Abstract Landiolol is a new ultra-short-acting beta 1-selective adrenoreceptor antagonist, which is metabolized rapidly by plasma cholinesterase (PCHE). Metoclopramide has been shown to inhibit PCHE in vitro. Therefore, metoclopramide might prolong beta blocking effects of landiolol and spoil its ultimate-short-acting property. Just before induction of anesthesia, gynecological patients were randomly assigned to receive 0.2 mg/0.1 ml/kg landiolol and 2 ml saline (Landiolol group; $n = 20$), 0.2 mg/0.1 ml/kg landiolol and 10 mg metoclopramide/2 ml solution (Landiolol-M group; $n = 20$), or 0.1 ml/kg saline and 2 ml saline (Control group; $n = 20$). Tracheal intubation was performed 3 min after induction of anesthesia. Heart rate and blood pressure were recorded. Landiolol with or without metoclopramide similarly inhibited increase in heart rate after induction of anesthesia and tracheal intubation. However, changes in blood pressure were not affected. Metoclopramide at induction of anesthesia did not prolong duration of action of landiolol attenuating the hemodynamic response to induction of anesthesia and tracheal intubation.

Keywords Landiolol · Metoclopramide · Induction of anesthesia

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Introduction

Landiolol is a new ultra-short-acting beta 1-selective adrenoreceptor antagonist, which is now being widely used in Japan. It has a shorter plasma half-life (4 min) and less cardioselectivity than esmolol and has also been reported to effectively stabilize hemodynamic response during anesthetic induction [1–4]. It has been shown to be metabolized rapidly by plasma cholinesterase (PCHE) [5]. Metoclopramide has been shown to inhibit PCHE in vitro [6–9]. Its use for preventing postoperative nausea and vomiting in perioperative settings is popular among anesthesiologists although the effect of this drug for that purpose is controversial [10]. Neuromuscular block caused by succinylcholine and mivacurium, which are also metabolized by PCHE, has been shown to be prolonged by 23 and 30% after metoclopramide 10 mg iv before induction of anesthesia [7, 11]. Therefore, metoclopramide might prolong beta blocking effects of landiolol and spoil its ultimate-short-acting property. In this study, we investigated whether co-administration of metoclopramide at induction of anesthesia can prolong duration of action of landiolol attenuating the hemodynamic response to induction of anesthesia and tracheal intubation.

After institutional approval and informed consent, 60 patients scheduled for gynecological procedures in the supine position were enrolled. Patients with symptomatic ischemic heart disease, or who were administered vasodilator were excluded.

No patients were premedicated. On arrival in the operating room, routine monitors were applied, including electrocardiogram, noninvasive blood pressure cuff, pulse oximetry, and capnogram. A 20-gauge catheter was inserted into a left forearm vein for fluid and drug administration. Acetate Ringer's solution was administered at

10 ml kg^{-1} h^{-1} during the study period. Before induction of anesthesia, an epidural catheter was inserted at the 11–12th thoracic interspace and placed 5 cm beyond the introducer needle tip. Three milliliters of epinephrine-containing (1:100000) 1% lidocaine was used to deny unintentional intravascular or intrathecal catheter placement. No more local anesthetic was used during the study period. Just before induction of anesthesia, patients were randomly assigned (closed envelope technique) to receive 0.2 mg/0.1 ml/kg landiolol and 2 ml saline (Landiolol group; $n = 20$), 0.2 mg/0.1 ml/kg landiolol and 10 mg metoclopramide/2 ml solution (Landiolol-M group; $n = 20$), or 0.1 ml/kg saline and 2 ml saline (Control group; $n = 20$). These doses were determined on the basis of previous studies which investigated effects of beta-blockers on laryngoscopy and tracheal intubation (0.1–0.3 mg/kg for landiolol) [1–4]. Attendant anesthesiologists were unaware of the test drugs. Subsequently, anesthesia was induced with propofol 1.5–2.5 mg/kg, fentanyl 1–2 μg/kg, and vecuronium 0.1 mg/kg. Atropine 0.01 mg/kg was simultaneously administered to prevent cholinergic response. Anesthesia was maintained with 3% end-tidal sevoflurane in oxygen until tracheal intubation, which was performed 3 min after induction of anesthesia. Anesthesia was then maintained with 2% end-tidal sevoflurane in 40% oxygen, supplemented with doses of fentanyl and vecuronium.

Heart rate and blood pressure were measured just before induction of anesthesia and every 1 min afterward for 10 min. During the following 10 min, these values were recorded every 5 min.

Statistical analysis

The study population size was determined on the basis of the following hypothesis. We assumed that the depressive effect of landiolol against tracheal intubation can be prolonged by 25% after metoclopramide injection. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.9, 18 patients in each group were required. Thus, we included 20 patients in each group for the study population size.

Comparisons of changes in hemodynamic variables and temperatures among the groups were performed by using analysis of variance for repeated measures followed by Bonferoni test. Other comparisons among the groups were carried out using analysis of variance followed by the Bonferoni test for continuous variables, and the Chi-square test for nominal data. Data are expressed as mean ± standard deviation (SD) of the mean; differences were considered significant when $p < 0.05$.

Because of failure of measurement of hemodynamic valuables, 1 patient in the control group and 1 in the Landiolol group were excluded from the study. Patient characteristics are shown in Table 1. The values were similar among the three groups. Figures 1 and 2 show the intraoperative changes in heart rate and mean arterial blood pressure. Landiolol with or without metoclopramide similarly inhibited increase in HR after induction of anesthesia and tracheal intubation (from 1 to 6 min after induction of anesthesia). However, landiolol with or without metoclopramide did not affect changes in MAP.

The results from this study showed that landiolol with or without metoclopramide similarly affected the hemodynamic response to induction of anesthesia and tracheal intubation. Therefore, the hypothesis was rejected that co-administration of metoclopramide at induction of anesthesia can prolong the duration of action of landiolol attenuating the hemodynamic response to induction of anesthesia and tracheal intubation.

Landiolol is a newly developed highly cardioselective beta-blocker with a high potency ratio (beta-1/beta-2). In addition, landiolol has a short duration of activity (a half-life of 4 min), enabling rapid recovery after cessation of administration, through rapid hydrolysis of its ester linkage [5]. There was, therefore, a possibility that its duration of

Table 1 Patient characteristics

	Control ($n = 19$)	Landiolol ($n = 19$)	Landiolol-M ($n = 20$)	p value
Age (years)	59 ± 15	54 ± 14	54 ± 14	0.414
Weight (kg)	56 ± 10	60 ± 8	58 ± 10	0.365
Height (cm)	156 ± 7	159 ± 7	160 ± 6	0.266
Hemoglobin (g/dl)	10.1 ± 0.9	10.2 ± 0.8	10.2 ± 0.9	0.919
Anesthesia time (min)	146 ± 28	151 ± 28	157 ± 23	0.463
Operation time (min)	106 ± 24	112 ± 25	123 ± 30	0.132
Infusion (ml)	1467 ± 208	1440 ± 206	1551 ± 204	0.223
Transfusion (ml)	263 ± 171	316 ± 108	282 ± 146	0.264
Urine (ml)	240 ± 110	236 ± 93	266 ± 96	0.519
Blood loss (ml)	292 ± 115	292 ± 166	267 ± 167	0.605

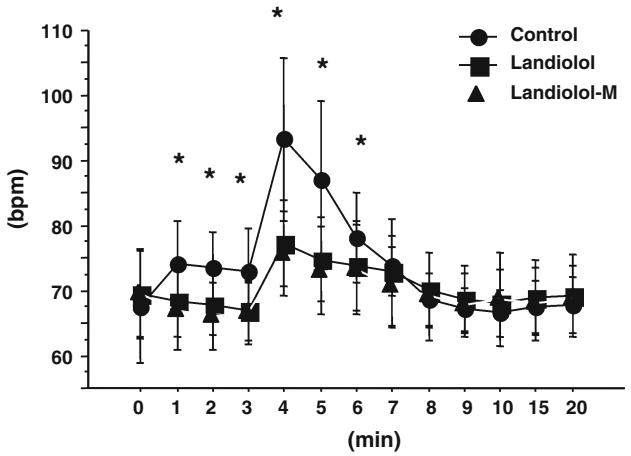

Fig. 1 Changes in heart rate. The data are expressed as mean ± standard deviation (SD). *$p < 0.05$ or 0.01, the control group versus the landiolol and landiolol-M groups

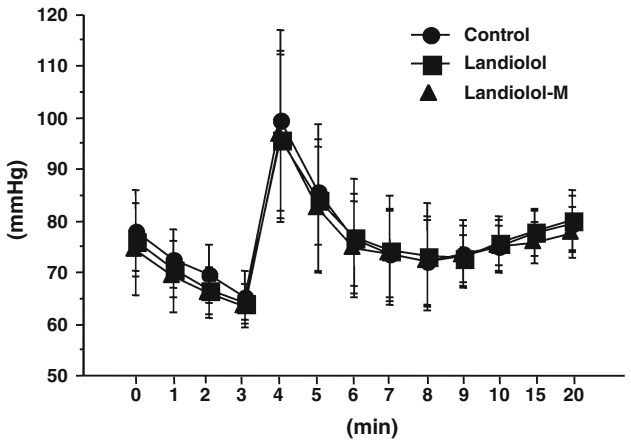

Fig. 2 Changes in mean arterial pressure. The data are expressed as mean ± standard deviation (SD)

beta-blocking action was prolonged by inhibiting PCHE activity. As mentioned before, metoclopramide has been shown to inhibit PCHE in vitro and in vivo [6–9]. In fact, neuromuscular block caused by succinylcholine and mivacurium, which are also metabolized by PCHE, has been shown to be prolonged by 23 and 30% after metoclopramide administration before induction of anesthesia [7, 11]. Thus, we initially hypothesized that metoclopramide would prolong the duration of action of landiolol at least by 25%; however, prolongation of its duration of action by metoclopramide was not observed in this study.

From previous studies, it can be expected that PCHE activity should be inhibited by 10–20% after administration of 10 mg metoclopramide [6–9]. Therefore, it is reasonable to think that PCHE activity in this study was inhibited by 10 mg metoclopramide to the same extent as in previous reports, although PCHE activity was not determined in this study. Why was the duration of action of landiolol not prolonged at all in this study? The most likely reason is that co-administered anesthetics could mask the after effects of landiolol, attenuating the hemodynamic response to induction of anesthesia and tracheal intubation. Propofol, fentanyl, and sevoflurane, which have more or less negative circulatory effects, were used as induction drugs. In addition, the hemodynamic response to induction of anesthesia and tracheal intubation usually lasts very briefly. Actually, HR and MAP in the control group in this study returned to the baseline values in 4–5 min after tracheal intubation. At this time point, effects of induction drugs might have affected hemodynamic status more than landiolol if duration of action of landiolol could have been prolonged by metoclopramide. To address this concern, effects of metocroplamide on duration of action of landiolol might have to be evaluated in the absence of these induction drugs. Otherwise, as another explanation, the effect of metoclopramide on prolongation of landiolol's action (i.e. decrease in heart rate) could be masked by another action of this compound—it can increase heart rate independently of levels of plasma cholinesterase, because previous studies have demonstrated that, in an animal model, metoclopramide exaggerates stress-induced tachycardia [12] and that it induced supraventricular tachycardia in clinical practice [13]. However, we cannot provide an appropriate answer regarding this concern because we did not evaluate a sole effect of metoclopramide in this study.

There are two issues about which we have to make comments. Obviously, the question will no doubt be raised whether there is a clinical significance regarding 25% prolonged action of landiolol. In answer to this question, we have to say "no" because duration of action of landiolol can be similar to that of esmolol, which is also a short-acting cardioselective beta-blocker, even though its action would be prolonged by 25% [3, 14]. However, we believe that most anesthesiologists are interested in the possibility that a commonly used drug can have an interaction with a newly developed ultra-short acting beta-blocker. The other fundamental issue though, is that the study implies a pharmacokinetic effect yet no serum samples were measured. Instead the pharmacodynamic response of HR is used as a surrogate measure in this study. The final concern is that we did not have any answer to the question whether metoclopramide prolonged the duration of landiolol. As mentioned above, further studies are required; however, we believe that it is clinically significant that our report showed no effect of metoclopramide on the action of landiolol during anesthesia induction and tracheal intubation.

In conclusion, landiolol with or without metoclopramide similarly affected the hemodynamic response to induction of anesthesia and tracheal intubation. Therefore, we concluded that metoclopramide at induction of anesthesia did

not prolong duration of action of landiolol attenuating the hemodynamic response to induction of anesthesia and tracheal intubation.

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