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ORIGINAL ARTICLE

Inhibitory effects of landiolol and nicardipine on thiopental-induced yawning in humans

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Abstract
Purpose Either the calcium (Ca^{2+})-channel blocker nicardipine or the β_1-adrenoceptor antagonist landiolol may be intravenously (IV) administered to reduce the hemodynamic responses to tracheal intubation. In this study, we examined the effects of these drugs on the yawning response elicited by intravenous thiopental in humans.
Methods After Institutional Review Board approval, 180 consenting American Society of Anesthesiologists (ASA) I or II patients undergoing elective surgery were recruited. In a double-blind, randomized design, three groups of 60 patients each received one of the following intravenous injections: (1) landiolol 0.1 mg/kg (L-group), (2) nicardipine 0.02 mg/kg (N-group), or (3) saline (S-group). In all patients, anesthesia was subsequently induced IV with 4 mg/kg thiopental. Thereafter, the occurrence of the yawning response (characterized by mouth opening) was continuously assessed as the only clinical endpoint for 1 min. Throughout the study, mean arterial blood pressure and heart rate were also recorded at 1-min intervals.
Results The incidence of the yawning response was lower in both the L-group (6.7%) and the N-group (16.7%) than in the S-group (46.7%) (each, $P < 0.01$).
Conclusions Prior intravenous administration of either a Ca^{2+}-channel blocker or a β_1-adrenoceptor antagonist can greatly reduce the thiopental-induced yawning response in humans.

Keywords Yawning · Anesthetic · Intravenous · Thiopental · Calcium-channel antagonist · Nicardipine · β_1-adrenoceptor antagonist · Landiolol

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Introduction

One of the most frequently encountered clinical situations during which yawning occurs is the IV induction of general anesthesia. Without prior administration of an opioid, such as fentanyl, a yawning response may occur within 1 min after IV injection of thiopental or propofol (occurrence rate approximately 50%) [1–3]. Moreover, we recently demonstrated in humans that this type of yawning is associated with a transient arousal shift during continuing loss of consciousness [2]. Either a β_1-adrenoceptor blocker or a calcium-channel antagonist or both has been adjunctively administered to reduce the hemodynamic response to tracheal intubation during the induction of general anesthesia [4–6]. Interestingly, in animal experiments using male rats, calcium-channel blockade has been demonstrated to prevent the yawning response [7], and how β-adrenoceptor antagonism affects this behavioral response is controversial [8, 9]. However, there are still no data regarding the effects of these pharmacological modulations on the occurrence of yawning in humans.

This study explored whether prior administration of either the highly selective β_1-adrenoceptor blocker landiolol or the calcium-channel antagonist nicardipine might alter the incidence of the yawning response elicited by IV

injection of thiopental in humans. Positive findings could provide insights into the physiologic and pharmacological aspects of yawning in humans.

Materials and methods

One hundred and eighty adult patients [each of the American Society of Anesthesiologists (ASA) physical status 1–2 and scheduled for elective surgery under general anesthesia] participated in this study, which was approved by the Institutional Review Board, at Gifu Red Cross Hospital. All patients gave prior written informed consent. Exclusion criteria were as follows: (a) renal, hepatic, or neurologic dysfunction, (b) use of benzodiazepines, anticonvulsants, alcohol, opioids, or other psychotropic drugs (chronically or within 24 h before the induction of anesthesia), and (c) any patient in whom a rapid sequence induction was indicated. A randomization list was generated, and based on this list, identical syringes each containing one of the test solutions were prepared by personnel who were not involved in this study. The patients were divided using a randomized, double-blind design into three groups of 60 patients each. They received one of the following IV-injected test solutions at 1 min before IV administration of thiopental: (1) landiolol 0.1 mg/kg (L-group), (2) nicardipine 0.02 mg/kg (N-group), and (3) saline (S-group).

No premedicant drugs were administered, and standard anesthetic regimens and techniques were employed for all patients. Routine monitors consisted of an automated blood-pressure cuff, electrocardiogram, and pulse oximeter. After obtaining baseline values and oxygenation through the mask, one of the aforementioned test solutions was given IV. One minute later, an IV injection of 4 mg/kg thiopental was administered by the investigator over a 5-s period. As the only clinical end point, three observers (blinded regarding the test solutions administered) continuously assessed the occurrence of the yawning response (characterized by mouth opening) after the start of the anesthetic infusion. The end of the 1-min observation period represented termination of this study. Then, vecuronium (0.16 mg/kg) was administered IV, and mask-assisted ventilation with 100% oxygen was applied until tracheal intubation. Throughout the study, mean arterial pressure (MAP) and heart rate (HR) were also recorded at 1-min intervals.

Group data are presented as the mean ± standard deviation (SD) or as number (%). $P < 0.05$ was considered statistically significant. Two-by-three frequency tables were constructed, cross-tabulating the occurrence rate of the yawning response against the S-, N-, and L-groups, and these were analyzed by means of Fisher's exact probability test. Continuous data, including demographics and hemodynamics for all patients were analyzed with Bonferroni's multiple-comparison test after a one-way analysis of variance. Power analysis was performed to determine the number of patients that should be enrolled in the study based upon the following assumptions: (1) incidence of yawning in the S-group would be 50%, (2) a change from 50% to 25% in either the N- or L-group would be considered clinically significant, and (3) $\alpha = 0.05$, and $1 - \beta = 0.8$. On the basis of these assumptions, at least 50 patients per group were required.

Results

There were no significant differences among the L-, N-, and S-groups in terms of age, sex, height, weight, baseline MAP, or baseline HR (Table 1). The incidence of the thiopental-induced yawning response was lower in both the L-group (6.7%) and the N-group (16.7%) than in the S-group (46.7%) (each, $P < 0.01$) (Table 1). After IV administration of the test solutions (saline or a test drug), two differences were observed among the three groups in terms of hemodynamics. As shown in Fig. 1, one was the lower MAP in the N-group after administration of the test solutions ($P < 0.01$ vs. the other two groups). As demonstrated in Fig. 2, the other was the rank order of the groups (L < S < N) in terms of HR ($P < 0.01$ for each comparison). In contrast, changes in MAP and HR following IV administration of thiopental were similar among the three groups (Table 2).

Table 1 Summary of patient characteristics in the landiolol (L), nicardipine (N), and saline (S) groups

	L-group ($n = 60$)	N-group ($n = 60$)	S-group ($n = 60$)
Age (year)	40.3 ± 12.0	41.4 ± 13.2	45.3 ± 9.4
Male/female	22/38	24/36	20/40
Height (cm)	161.1 ± 7.4	161.7 ± 8.6	158.8 ± 7.8
Weight (kg)	57.7 ± 9.3	60.2 ± 11.1	56.2 ± 9.7
Baseline MAP (mmHg)	90.1 ± 9.9	103.5 ± 16.1	97.9 ± 13.7
Baseline HR (min^{-1})	79.0 ± 14.2	81.8 ± 19.9	86.7 ± 20.4
Yawning (%)	6.7*	16.7*	46.7

MAP mean arterial pressure, *HR* heart rate

* $p < 0.01$ compared with S-group (for yawning)

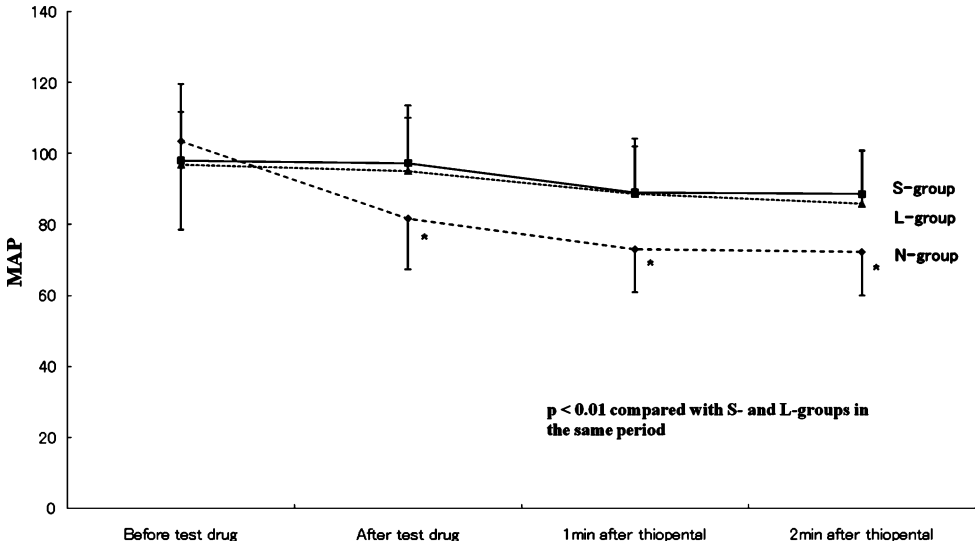

Fig. 1 Changes in mean arterial pressure (MAP) during intravenous anesthesia induction in the landiolol (L), nicardipine (N), and saline (S) groups

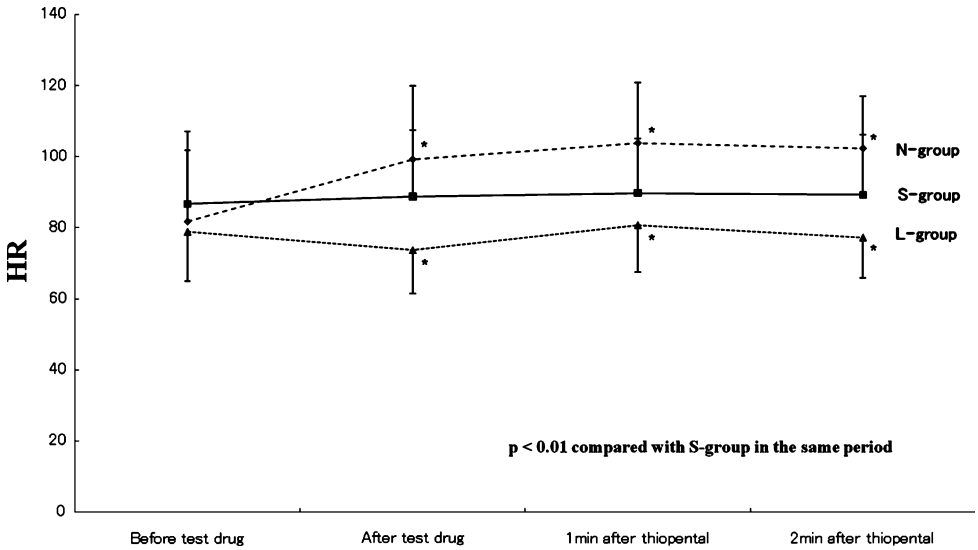

Fig. 2 Changes in heart rate (HR) during intravenous anesthetic induction in the landiolol (L), nicardipine (N), and saline (S) groups

Table 2 Changes in mean arterial pressure (MAP) and heart rate (HR) after intravenous administration of thiopental in the landiolol (L), nicardipine (N), and saline (S) groups

	L-group	N-group	S-group
MAP	−6.4 ± 10.8	−8.7 ± 12.7	−8.3 ± 10.8
HR	7.0 ± 9.9*	4.6 ± 11.8	0.9 ± 10.6

* $p < 0.01$ compared with S-group (for HR)

Discussion

Our main finding was that in patients undergoing IV induction of general anesthesia, prior IV administration of either landiolol or nicardipine significantly reduced the incidence of the thiopental-induced yawning response. This indicates that the incidence of thiopental-induced yawning response can be greatly reduced by a blockade of either β_1-adrenoceptors or calcium channels in humans.

The neurochemical mechanism of yawning is briefly reviewed. The paraventricular nucleus (PVN) of the hypothalamus is essential for spontaneous yawns, because microinjection of several substances, including apomorphine [10], L-glutamate, or NOC-7 as a nitric-oxide-releasing compound [11] into the PVN increases the frequency of spontaneous yawns. Furthermore, Sato-Suzuki and coworkers demonstrated that the stereotyped yawning responses evoked by microinjection of these drugs into the PVN are mediated by nitric oxide synthase-positive oxytocinergic parvocellular neurons in the PVN projecting to the lower brain stem and the spinal cord [11]. As to the neurochemical mechanism through which microinjection of L-glutamate into the PVN induces the stereotyped yawning response, Melis and Argiolas [12] provided the most plausible explanation that activation of N-methyl-D-aspartic acid (NMDA) receptors increases intracellular calcium (Ca^{2+}) concentration in cell bodies of

oxytocinergic neurons in the PVN, mediating this behavioral response by increasing Ca^{2+} influx through Ca^{2+} channels coupled to NMDA receptors. The increase in intracellular Ca^{2+} activates nitric oxide synthase to produce nitric oxide, thereby facilitating oxytocinergic transmission in the PVN of the hypothalamus [13]. Therefore, the neurochemical mechanism underlying the yawning responses both evoked by L-glutamate and nitric oxide may be a common one that is linked.

Inhibition of the yawning response by systemic β_1-adrenoceptor antagonism observed in our study may be related to opioid mimetic/sparing effects. Besides their cardioinhibitory effects, short-acting β1-adrenoceptors landiolol and esmolol are reported to exert antinociceptive and opioid mimetic/sparing effects in animals [14, 15] and humans [16, 17]. For example, intrathecal administration of landiolol [14] and IV administration of esmolol [15] inhibit nociception in the mouse and rat formalin tests, respectively. Furthermore, intraoperative infusion of esmolol has been reported to be effective in sparing the required dose of opioids intraoperatively [16] and postoperatively [17] in humans. β-adrenoreceptors and opioid receptors, members of G-protein-coupled-receptor superfamily, are known to functionally and physically cross-talk via multiple hierarchical mechanisms, including heterodimerization of these receptors, counterbalance of functional opposing G-protein signaling, and interface at downstream signaling events [18]. On the other hand, the hypothetical mechanism by which IV-administered landiolol might suppress the thiopental-induced yawning response through an opioid mimetic/sparing effect is supported by our recent finding in humans that the probability of a thiopental-induced yawning response is decreased by prior use of IV-administered fentanyl [3]. Indeed, yawning is one of the commonest signs of opiate withdrawal syndrome in opiate addicts. In rats, however, the situation is less clear, as systemic administration of β-adrenoceptor antagonists such as propranolol and pindolol has been reported either to potentiate the yawning response [8] or to have no effect on it [9]. Although these inconsistent results may be attributed to either species-related differences or the roles of β_1- and β_2-adrenoceptor subtypes associated with the central pattern generator for yawning with particular reference to opioid mimetic/sparing effects, or both, the inhibitory mechanism of yawning by landiolol will remain unclear until these problems are elucidated.

The effect induced by systemic calcium-channel blockade demonstrated in this study supports a possible role for thiopental-induced Ca^{2+} influx into the cell bodies involved in the central pattern generator for yawning in humans, which is consistent with the results obtained from in vitro experiments using dog cerebral arteries [19] and rat aortic smooth muscle [20]. If we can extrapolate from the aforementioned neurochemical mechanism of yawning, thiopental may, in humans, induce an intracellular Ca^{2+} increase that activates nitric oxide synthetase, thereby producing nitric oxide, and this in turn may activate oxytocinergic transmission in the PVN of the hypothalamus [13], leading to yawning.

In this study, two distinct hemodynamic differences were observed among the three groups after IV administration of the test solutions. These differences (viz. a lower MAP following nicardipine and the rank order landiolol < saline < nicardipine for HR) are consistent with several previous reports regarding the effects of esmolol and nicardipine on the hemodynamic reaction to tracheal intubation [4, 5]. Despite these hemodynamic differences in our study, changes in MAP and HR observed after IV-administered thiopental did not differ among the three groups. Sato-Suzuki and colleagues previously demonstrated in the anesthetized, spontaneously breathing rat that a fall in systemic blood pressure always precedes yawning behavior [11]. On that basis, the falls in MAP seen following IV-administered thiopental might be expected to be closely related to yawning. However, our results suggest that the inhibitory effect of neither landiolol nor nicardipine on the yawning response is attributable to its hemodynamic effects. On the other hand, these hemodynamic differences (viz. a lower MAP following nicardipine and the rank order landiolol < saline < nicardipine for HR) may deteriorate the blindness of the test drugs in this study.

Aside from the test solutions they were given, we believe that there were no significant differences in the risk factors affecting the incidence of thiopental-induced yawning among our L-, N-, and S-groups. No patient in any group received prior opioid administration, such as IV-administered fentanyl or remifentanil, or clonidine premedication. Furthermore, there were no significant differences in gender among the three groups.

In conclusion, IV administration of either landiolol or nicardipine (prior to anesthesia induction) reduced the incidence of the thiopental-induced yawning response in humans. The inhibitory effects of these drugs on the yawning response may be attributable to a blockade of β_1-adrenoceptors or calcium channels per se, respectively.

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