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ORIGINAL ARTICLE

The effects of intravenous anesthetics on QT interval during anesthetic induction with sevoflurane

Yoshiaki Terao[1] · Ushio Higashijima[1] · Tomomi Toyoda[1] · Taiga Ichinomiya[1] · Makoto Fukusaki[1] · Tetsuya Hara[2]

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Abstract
Purpose Sevoflurane is known to prolong the QT interval. This study aimed to determine the effect of the interaction between intravenous anesthetics and sevoflurane on the QT interval.
Methods The study included 48 patients who underwent lumbar spine surgery. Patients received 3 μg/kg fentanyl and were then randomly allocated to either Group T, in which they received 5 mg/kg thiamylal, or Group P, in which they received 1.5 mg/kg propofol, at 2 min after administration of fentanyl injection for anesthetic induction. Vecuronium (1.5 mg/kg) and sevoflurane (3 % inhaled concentration) were administered immediately after loss of consciousness and tracheal intubation was performed 3 min after vecuronium injection. Heart rate (HR), mean arterial pressure (MAP), bispectral index score (BIS), and the heart rate-corrected QT (QTc) interval on a 12-lead electrocardiogram were recorded immediately before fentanyl administration (T1), 2 min after fentanyl injection (T2), immediately before intubation (T3), and 2 min after intubation (T4).
Results There were no significant differences between the two groups in baseline patient characteristics. BIS and MAP significantly decreased after anesthesia induction in both groups. At T3, MAP in Group T was higher than in Group P, while HR had reduced in both groups. The QTc interval was prolonged after anesthesia induction in Group T, but did not change at any time point in Group P. The QTc interval after anesthesia induction in Group T was longer than in Group P.
Conclusion We concluded that an injection of propofol could counteract QTc interval prolongation associated with sevoflurane anesthesia induction.

Keywords Propofol · Sevoflurane · Thiamylal · QT interval · QT dispersion · Dysrhythmias

Introduction

The QT interval of the electrocardiogram (ECG) represents the period of myocardial depolarization and repolarization. Heart rate-corrected QT (QTc) interval prolongation is associated with life-threatening dysrhythmias, including polymorphic ventricular tachycardia (torsade de pointes), and it is important to know which anesthesia patients are at risk of prolonged QTc interval. Volatile anesthetics, including sevoflurane, are known to prolong the QT interval significantly [1], and thiamylal can also cause marked prolongation of the QT interval [2]. We previously reported that intravenous propofol can shorten the QTc interval during anesthesia induction [2, 3], while Kleinsasser et al. further reported that sevoflurane-associated QTc interval prolongation was reversed within 15 min after substituting propofol for sevoflurane [4]. Propofol injection also counteracted QTc interval prolongation induced by an antiemetic dose of droperidol during anesthesia induction [5]. However, propofol is generally used as an induction agent before sevoflurane administration, and it appears that the

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✉ Yoshiaki Terao
yoterao@na-robyo.jp

[1] Department of Anesthesia, Nagasaki Rosai Hospital, 2-12-5 Setogoe, Sasebo 857-0134, Japan

[2] Department of Anesthesiology, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

preventative effect of propofol on sevoflurane-induced QTc interval prolongation has not been previously examined.

QT dispersion (QTD) is the difference between the maximum and minimum QT intervals on a 12-lead ECG, and is regarded as a measure of left ventricular repolarization inhomogeneity that could represent an electrophysiological index for increased risk of ventricular dysrhythmia [6]. Increased QTD is a sign of heterogeneous repolarization and possible arrhythmogenic re-entry [7]. Yildirim et al. reported that sevoflurane, isoflurane, and desflurane prolong QTc interval and QTcD [8], while Emin et al. found that sevoflurane and desflurane prolong QTc interval but do not influence QTD [9]. Our previous study showed that a bolus administration of propofol did not affect QTcD [2].

The aim of this open-label randomized clinical study was to determine the interaction between intravenous anesthetics and sevoflurane on QTc interval and QTcD during anesthesia induction.

Methods

Patients

This open-label randomized clinical trial included 48 American Society of Anesthesiologists (ASA) physical status I or II patients aged 20–79 years who underwent elective lumbar spine surgery, including laminectomy, microscopic discectomy, microendoscopic discectomy, or spinal fusion, under general anesthesia between July 2007 and March 2008. The study protocol was approved by the Institutional Research and Ethics Committee, and written informed consent was obtained from each participant. The exclusion criteria included a medical history of diabetes, ischemic heart disease, preoperative ECG abnormalities, and preoperative medications known to prolong the QTc interval, including β-adrenergic antagonists and antiarrhythmic agents. None of the patients received any preanesthetic medication.

Study protocol

Pulse oximetry, 3-lead ECG, non-invasive blood pressure (BP) monitoring, and bispectral index score (BIS) measurement (A2000 BIS Monitoring System; Aspect Medical System, Natick, MA, USA) were performed as the standard procedure for patients receiving general anesthesia. The incidence of dysrhythmia was monitored by continuous recording of ECG lead II. The 12-lead ECG was attached to the patients before anesthesia induction, and the standard 12-lead ECG recordings were obtained at each pre-specified measurement time with a computerized ECG recorder (model FX-7432; Fukuda Denshi, Tokyo, Japan) at a paper speed of 25 mm/s. The ECG data were also recorded digitally. QT intervals were measured by using developed software (QTD-1; Fukuda Denshi, Tokyo, Japan), which is programmed to detect the onset of the QRS complex and the end of the T wave [2, 10].

The QTc interval was calculated according to Fridericia's formula [11] as follows:

$$\mathrm{QTc} = \mathrm{QT}/\sqrt[3]{\mathrm{RR}}.$$

The data were excluded from analysis in cases where the QT interval could not be reliably measured because of T-wave morphology and a 6-lead minimum was considered necessary for the analysis. QTcD was defined as the difference between the maximum and minimum QTc interval values in all leads. The mean QTc interval was calculated from all available QTc interval values averaged from three consecutive cycles in all leads during the measurement period. An investigator, who was blinded to the anesthetic agent, examined and analyzed the ECGs.

The patients were randomly divided by sealed envelope assignment into two groups—Group T ($n = 24$) and Group P ($n = 24$). All patients received oxygen via a facemask at a flow rate of 5 L/min for 2 min prior to an injection of 3 μg/kg fentanyl. The patients in Group T received 5 mg/kg thiamylal and those in Group P received 1.5 mg/kg propofol at 2 min after administration of fentanyl injection. Intravenous vecuronium (1.5 mg/kg) and inhaled sevoflurane (3 % inhaled concentration) were administered to all patients immediately after loss of consciousness and tracheal intubation was performed 3 min after administration of vecuronium injection. The eyelash reflex was continuously monitored after loss of verbal response, and loss of consciousness was defined as loss of the eyelash reflex [12]. The inhaled concentration of sevoflurane was decreased to 1 % after tracheal intubation in all patients and the respiratory rate was adjusted to maintain an end-tidal carbon dioxide partial pressure of 35 mmHg. Heart rate (HR), mean arterial pressure (MAP), BIS, end-tidal sevoflurane concentration (ETsevo), and 12-lead ECG were recorded immediately before fentanyl injection (baseline T1), 2 min after fentanyl injection (T2), 3 min after vecuronium injection (immediately before tracheal intubation; T3), and 2 min after tracheal intubation (T4).

Statistical analysis

The results are expressed as median [IQR (range)]. A 2-factorial analysis of variance with repeated measures was performed to analyze the interaction between time and the two groups. A post hoc comparison between groups at each time point and among the repeated measures in each group was performed using Bonferroni/Dunn procedure, if appropriate. Continuous data for patient characteristics were

Table 1 Patient characteristics

Variables	Thiamylal group	Propofol group	*p* value
Patients	24	24	
ASA I/II	16/9	18/7	0.63
Sex (male/female)	14/10	19/5	0.22
Age (years)	62 [53–67 (33–77)]	53 [41–65 (33–77)]	0.08
Height (cm)	160 [151–169 (142–177)]	166 [160–171 (140–180)]	0.07
Weight (kg)	63 [55–66 (43–80)]	64 [58–73 (43–83)]	0.23
BSA ($m^{2)}$	1.63 [1.53–1.73 (1.29–1.95)]	1.76 [1.59–1.80 (1.32–1.94)]	0.08
Sodium (mmol L^{-1})	142 [140–144 (138–146)]	142 [141–143 (138–146)]	0.98
Potassium (mmol L^{-1})	4.1 [4.0–4.3 (3.1–5.2)]	4.1 [3.9–4.3 (3.7–5.3)]	0.56
Calcium (mg dL^{-1})	9.2 [8.9–9.4 (8.8–10.1)]	9.3 [8.9–9.5 (8.6–9.7)]	0.88
Hemoglobin (g dL^{-1})	14.4 [13.2–15.1 (11.5–16.1)]	14.8 [13.5–15.2 (11.7–16.8)]	0.36

Values are number, median [IQR (range)]

ASA American Society of Anesthesiologists physical status, *BSA* body surface area

Table 2 Incidence of dysrhythmia

Variables	Thiamylal group	Propofol group	*p* value
APC/total (*n*)	0/24 (0 %)	0/24 (0 %)	0.99
VPC/total (*n*)	0/24 (0 %)	0/24 (0 %)	0.99

Values are number (%)

APC atrial premature contraction, *VPC* ventricular premature contraction

analyzed using the Mann–Whitney *U* test. Dichotomous variables were analyzed with either the Fisher's exact probability or chi-squared test. A *p* value of <0.05 was considered statistically significant.

Sample size was determined on the basis of the previous study (SD 23 ms) [2], which indicated that with 22 patients in each group a power of 90 % would be required to detect a difference of 23 ms in the mean QTc interval value between the two groups at a 5 % significance level.

Results

Fifty-one patients (35 men and 16 women) were enrolled in the study. Of these, 3 patients [2 men (one from each group) and 1 woman from Group T] were excluded because their ECG data were wrongly entered in the software. Therefore, 48 patients were included in the final analysis. None of the participants required vasopressors during the study. Table 1 shows the patient characteristics. There were no significant differences between the two groups.

Table 2 shows the incidence of dysrhythmia (premature atrial and ventricular contraction). There was no significant difference between the 2 groups.

Table 3 shows ETsevo, BIS values, and circulatory variables for both groups. There were no significant differences in ETsevo between the two groups. BIS and MAP were significantly decreased after anesthesia induction in both groups. HR was significantly decreased after anesthesia induction and recovered after tracheal intubation. There were no significant differences in QTcD at any recorded time point.

Figure 1 shows the QTc interval values for both groups at each time point. An analysis of variance indicated significant effects of both intravenous agent ($p < 0.0027$) and time ($p < 0.0001$). The interaction between the intravenous agent and the time point was also significant ($p < 0.0001$). These findings were confirmed by post hoc testing. In Group T, the QTc interval values at T3 ($p < 0.0001$) and T4 ($p < 0.0001$) were significantly prolonged compared with the QTc interval at T1. The QTc interval did not change over time in Group P, and the QTc interval at T3 ($p < 0.0001$) and T4 ($p = 0.0006$) in Group T were significantly longer than in Group P.

Discussion

The propofol injection seemed to counteract QTc interval prolongation associated with sevoflurane anesthesia induction, while neither intravenous anesthetic agent affected QTcD.

We previously found that propofol shortens the QTc interval [2, 3], although these findings were inconsistent with those of Kim et al. [13]. This discrepancy might be explained by the following. First, our data on QT intervals were collected from averaged leads, whereas Kim et al. obtained their data from a single lead. Second, we used Fridericia's formula, whereas Kim et al. used Hodges formula. Third, we evaluated the depth of anesthesia according to the accepted BIS for adequate depth of anesthesia, whereas Kim et al. used target-controlled infusion of propofol with

Table 3 Comparison of selected variables in thiamylal and propofol groups

Variable	Groups	T1	T2	T3	T4
ETsevo (vol %)	Thiamylal			1.7 (1.6–2.0 (1.4–2.3)]	1.1 [1.0–1.2 (0.9–1.2)]*
	Propofol			1.7 [1.6–1.8 (1.4–2.0)]	1.0 [0.9–1.2 (0.7–1.3)]*
BIS	Thiamylal	96 [90–97 (61–95)]	95 [89–97 (70–98)]	41 [29–62 (24–80)]*	51 [40–59 (22–64)]*
	Propofol	93 [90–97 (54–98)]	92 [84–97 (37–98)]	40 [37–46 (29–67)]*	44 [39–48 (29–58)]*
HR (min^{-1})	Thiamylal	63 [56–78 (48–108)]	66 [55–88 (48–103)]	60 [54–66 (46–73)]*	63 [57–72 (51–99)]
	Propofol	66 [58–81 (49–105)]	63 [57–76 (49–101)]	57 [50–66 (48–91)]*	64 [56–75 (46–99)]
MAP (mmHg)	Thiamylal	101 [94–112 (71–130)]	98 [93–107 (66–141)]	79 [65–88 (56–97)]*	87 [70–103 (58–115)]*
	Propofol	99 [92–108 (85–134)]	99 [93–106 (77–125)]	62 [56–67 (39–121)]†,*	73 [65–82 (47–140)]*
QTcD (ms)	Thiamylal	45 [40-–53 (26–74)]	39 [29–49 (20–74)]	38 [31–47 (26–62)]	47 [35–60 (22–90)]
	Propofol	41 [37–52 (25–77)]	35 [28–46 (21–79)]	45 [32–53 (19–76)]	47 [30–58 (23–74)]

Values are median [IQR (range)]

T1 baseline, *T2* 2 min after fentanyl, *T3* 3 min after vecuronium, *T4* 2 min after intubation, *ETsevo* end-tidal sevoflurane concentration, *BIS* bispectral index score, *HR* heart rate, *MAP* mean arterial pressure, *QTcD* heart rate-corrected QT interval dispersion

* $p < 0.05$ vs T1 values or T3 values (in ETsevo); † $p < 0.05$ vs thiamylal group

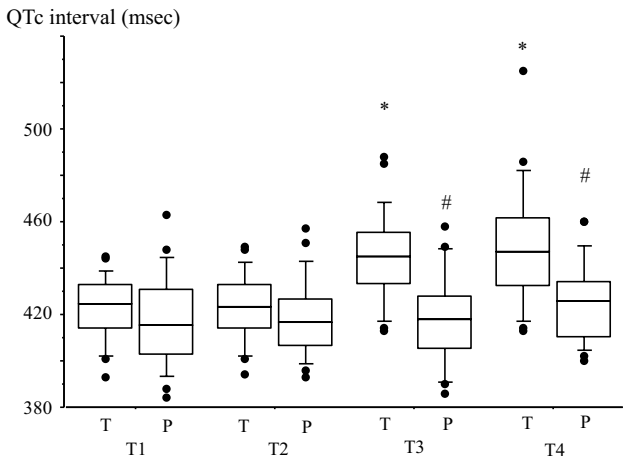

Fig. 1 Heart rate-corrected QT (QTc) interval in the thiamylal and propofol groups at each time point. Values are expressed as median (*line* inside the *boxes*), IQR (*boxes*), and 10–90 percentiles (*whiskers*). *T* thiamylal group, *P* propofol group, *T1* baseline, *T2* after fentanyl injection, *T3* 3 min after vecuronium injection (immediately before intubation), *T4* 2 min after intubation; *$p < 0.05$ vs T1 values; #$p < 0.05$ vs thiamylal group

an effect-site concentration of 5 μg/mL for 15 min without BIS. Fourth, we added a bolus dose of fentanyl to counteract the stimulus of tracheal intubation during anesthetic induction.

We chose to use average values from the 12-lead ECG because of inter-lead variations in the QT interval [14]. Bazett's formula is most widely used for heart rate correction but is known to overcorrect the QT interval and can lead to a false diagnosis of prolonged QTc interval [11]. The Hodges and Fridericia's formulae showed similar rate dependence of the QTc interval at both slower and faster heart rates in patient groups with normal and prolonged QT intervals [15]. In this study, the QT interval was corrected for heart rate using Fridericia's correction in accordance with guideline E14 of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [16].

Changes in the QTc interval reflect the effects of drugs and depth of anesthesia on the ionic currents in cardiac myocytes. There are at least 6 distinct potassium currents in cardiac myocytes [17], with the delayed rectifier (I_K) and inward rectifier (I_{K1}) currents being the main ones. I_{K1} is the prime determinant of resting conductance of cardiac myocytes and I_K is the key determinant of action potential duration (APD). The I_K current consists of a rapid component (I_{Kr}) and a slow component (I_{Ks}). Volatile anesthetics are known to cause I_K current inhibition [7]. I_K inhibition prolongs repolarization of the myocytes, and therefore prolongs the QT interval. However, each volatile anesthetic affects the I_{Kr} and I_{Ks} channels differently, resulting in varying degrees of QT prolongation. Sevoflurane has been shown to inhibit I_{Ks} channels in guinea pig ventricular cells, which contributes significantly to prolonged APD [18]. QTc interval changes correlate with sevoflurane concentration at clinically relevant doses [19]. Although the major electrophysiological action of sevoflurane appeared to be suppression of I_K, sevoflurane had a relatively modest suppressive action to L-type calcium currents (I_{Ca}) [20].

On the other hand, intravenous propofol at 5 μg/mL (28 μM) caused significant I_K depression but had no effect on I_{K1} [17], and it also caused concentration-dependent I_{Ks} inhibition in guinea-pig ventricular myocytes without I_{Kr} inhibition [21]. In addition, propofol predominantly suppresses I_{Ca} in a concentration-dependent manner and shortens APD [21], and the QTc interval was shortened with

propofol at a concentration of 30 μM in rabbit myocytes [22]. The IC50 for the inhibitory effects of propofol on I_{Ks} and I_{Ca} were 23 and 9.8 μM, respectively [21]. The anesthetic effect of propofol is maintained in humans at blood concentrations ranging from 3.4 (19 μM) μg/mL to 4.5 (25 μM) μg/mL [22]. However, it is essential to take blood protein binding into account because this can reduce the free aqueous and effective concentration of propofol [23]. If protein binding is taken into account, the clinically relevant concentration of propofol is <2 μM [24]. The direct effect of propofol on cardiac ion channels might be weak in the clinically relevant concentration and other mechanisms, including the autonomic nervous system [22], can influence QTc interval during sevoflurane induction after propofol administration.

Kako et al. reported that dexmedetomidine administration after anesthesia induction with sevoflurane shortened the QTc interval in pediatric patients [25], and Kleinsasser et al. reported that sevoflurane-associated QTc interval prolongation could be reversed with propofol [4]. Moreover, our previous research demonstrated that propofol injection could counteract QTc prolongation induced by an antiemetic dose of droperidol during anesthesia induction [5].

Sympathetic stimulation during laryngoscopy and intubation can exacerbate QTc interval prolongation and, in this study, premedication with fentanyl may have prevented QTc interval prolongation to some extent by attenuation of the sympathetic stimulus during intubation. Chang et al. [26] reported that pretreatment with 2 μg/kg fentanyl significantly diminished QTc interval prolongation when laryngoscopy and tracheal intubation were performed during propofol induction.

Previous studies have shown that QTcD is increased in patients with ischemic heart disease [27, 28], and that QTcD may be a predictor of dysrhythmic events in patients with congestive heart failure [29]. However, there have been conflicting reports on whether sevoflurane prolongs QTcD [8, 9]. Our previous studies showed that propofol or thiamylal with sevoflurane does not affect QTD in similar study populations [2, 3]. Together, these studies suggest that co-existing cardiac disease could influence QTcD during anesthesia induction.

The most important parameters of the torsadogenic property for a drug include QTD and transmural dispersion of repolarization (TDR) [30]. TDR is defined as T wave peak-to-end interval (Tp-e) and results from differences in the APD between the layers of the myocardium [30]. Although we measured QTcD, some articles in the literature showed the importance of Tp-e for the prediction of torsade de pointes [31, 32]. Sevoflurane increases the QT interval in a dose-dependent manner, but does not increase the TDR [7, 32]. Although a few cases of sevoflurane-associated torsade de pointes have been reported, multiple predisposing risk factors including certain electrolyte abnormalities, concomitant use of a QT-prolonging drug and co-existing cardiac disease, were present in each of these cases [7].

There are several limitations in the present study. Although manual measurement using a digitiser is a standard method to assess QT interval, we used QT automatic analysis software. This software is superior in reproducibility and has few differences with manual measurements [33]. Although we did not prove that 5 mg/kg thiamylal was equipotent to 1.5 mg/kg propofol, our previous study showed that using those doses of thiamylal and propofol decreased BIS to the same level during total intravenous anesthesia induction [2]. Although sevoflurane is known to prolong the QT interval significantly [1], we never actually measured the QT interval during anesthesia induction with sevoflurane alone in our study populations.

In conclusion, the present study showed that propofol, but not thiamylal, did not prolong the QTc interval during anesthesia induction with sevoflurane. On the other hand, propofol and thiamylal during anesthesia induction with sevoflurane did not affect QTcD. Thus, we believe that propofol is suitable for anesthesia induction with sevoflurane in patients with a risk factor of ventricular dysrhythmia.

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