Effects of intravenous bolus injection of emulsified isoflurane on QTc interval of healthy volunteers in Pharmacokinetics study

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Abstract: Emulsified isoflurane is a novel intravenous anesthetic, which is a lipid emulsion of isoflurane. As some drugs have a QTc-prolongation effect which can increase a risk of arrhythmia, this study was to evaluate the effects of emulsified isoflurane on the QTc interval. This was a single-center, randomized, single-blind, non-comparative study. Subjects were randomly allocated to receive an intravenous bolus injection of 22.63, 38.26, or 49.73 mg/kg emulsified isoflurane, respectively. Standard 12-lead electrocardiograms were recorded before administration and at 28 timepoints after administration. Blood samples and the end-tidal isoflurane concentrations were collected for pharmacokinetic analysis. The primary target variable was the QTcF change from baseline at each time point. A two-sided 90% confidence interval (CI) was calculated for a QTcF change from baseline at each timepoint. The maximal 90% CIs of the mean QTcF from the baseline for 22.63, 38.26 and 49.73mg/kg emulsified isoflurane were 2.52-21.18 ms, 15.66-35.90 ms, and 17.65-40.71 ms, respectively. Non-significant relationship was observed between QTcF and the plasma concentration (or the end-tidal isoflurane concentration). Single intravenous dose of emulsified isoflurane of the anticipated therapeutic dose or supra-therapeutic doses was associated with a potential dose-dependent and non-concentration-related QTc-prolongation effect.

Keywords: Emulsified isoflurane, QTc interval prolongation, novel anesthetic.

INTRODUCTION

The QT interval represents the duration of ventricular depolarization and subsequent repolarization, and is measured from the beginning of the QRS complex to the end of the T wave on the electrocardiogram (ECG). The prolongation of the QT interval can increase the risk of potentially fatal arrhythmias, torsades de pointes (TdP) in particular. TdP can degenerate into ventricular fibrillation, leading to sudden death (Roden, 2004; Yap, *et al*., 2003). So, it is recommended to conduct clinical studies to evaluate the potential of a new drug to delay cardiac repolarization according to the E14 guideline issued by the International Conference on Harmonisation (ICH) (ICH, 2005).

Due to its intensive relationship to the heart rate, the QT interval is usually corrected by some methods to obtain a less heart rate dependent value called "the QTc interval". But the most appropriate formula to evaluate the QTc interval is still under debate. Various corrected formulae have been recommended, of which Bazett's correction ($QTcB=QT/RR^{1/2}$) and Fridericia's correction ($QTcF=QT/RR^{1/3}$) are most widely employed (ICH, 2005; Rautaharju, *et al*., 2009).

Emulsified isoflurane (Yichang Humanwell Pharmaceutical Co., LTD, China) is a novel lipid-based formulation with an isoflurane concentration of 120 mg/ml in 30% lipid emulsion. After a bolus intravenous injection of emulsified isoflurane is given, isoflurane diffuses from the emulsion to its sites of action in the brain through the vasculature (Yang, *et al*., 2006).

Many inhaled anesthetics used in the clinical practice, such as halothane (Schmeling, *et al*., 1991), enflurane (Schmeling, *et al*., 1991), isoflurane (ICH, 2005; Yildirim, *et al*., 2004; Sun, *et al*., 2012; Guler, *et al*., 2001; Michaloudis, *et al*., 1996), sevoflurane (Yildirim, *et al*., 2004; Kleinsasser, *et al*., 2000) and desflurane (Yildirim, *et al*., 2004; Owczuk, *et al*., 2005), might prolong the QTc interval in various degrees. It was reported that life-threatening arrhythmia induced by the QTc interval prolongation also happened in inhalation anesthesia (Abe, *et al*., 1998). Among drugs used in anesthetic practice, some were withdrawn from the market or relegated to a second-line status (Roden, *et al*., 2004).

Considering the great significance of the QTc-prolongation effect in the safety evaluation for new drugs, the effects of emulsified isoflurane on the QTc interval were evaluated in the pharmacokinetic study.

MATERIALS AND METHODS

Subjects

The study was conducted in thirty healthy volunteers (15 men, 15 women), aged 18 to 45 years, with the Body

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Mass Index (BMI) of 19-24 kg/m^2. The volunteers were required to meet the following inclusion criteria: American Society of Anesthesiologists (ASA) Physical Classification System status of P1, heart rate (HR) 50-100 beats/min (bpm), systolic arterial pressure (SBP) 90-140 mmHg, pulse oxygen saturation (SpO_2) >95% when inspiring air, resting 12-lead surface ECG and routine laboratory tests normal. The volunteers had no history of alcohol or drug abuse and were non-smokers.

The exclusion criteria included: 1) Any history of allergy, especially to isoflurane or lipid emulsion; 2) Any suspected history of malignant hyperthermia in the volunteer or his/her relatives; 3) Prolonged QTcB interval (>450 ms for man, >470 ms for woman); 4) Hyperlipidemia; 5) Known or expected difficult airway; 6) Recent use of any drug within 2 weeks; 7) Recent participation in other clinical trials (within 1 month); 8) Pregnancy or lactation.

The study was conducted after receiving the approval by the Ethics Committee of West China Hospital, Sichuan University on 10 November 2010. This study complied with the Ethical Principles in the Declaration of Helsinki. The written informed consents were received from all the volunteers before their participation in this study.

Study design

This was a single-center, randomized, single-blind, non-comparative study to evaluate the effects of intravenous bolus injection of emulsified isoflurane on the QTc interval in the healthy volunteers.

The anesthetic effectiveness of intravenous emulsified isoflurane was defined as the score of 1 in the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) score (Responds only after painful trapezius squeeze) (Chernik, *et al*., 1990). All the volunteers were measured the MOAA/S scores per 15 seconds within the first 15 minutes after administration, then once per 30 seconds within the second 15 minutes after administration, finally once per minute within the subsequent 30 minutes after administration. In a previous phase I tolerability study, half of volunteers in 10.31 mg/kg group received MOAA/S scores of 1 and all volunteers reached for MOAA/S scores of 1 from 22.63mg/kg group. In this study, an anticipated therapeutic dose (22.63mg/kg) and supra-therapeutic dose (38.26 and 49.73 mg/kg) were designed. Thirty volunteers were randomized to receive an intravenous bolus dose of 22.63, 38.26, or 49.73mg/kg of emulsified isoflurane with a male/female ratio of 1:1 in each group. Randomization was generated by using a computer-generated random sequence by the Biostatistics Department of Institute of Drug Clinical Trial• GCP Center, West China Hospital, and only the volunteers were blinded to all information of the study drug.

They were fasted and water drinking was forbidden for 12 h before the treatment day. On the treatment day, an 18G venous catheter was placed in the median cubital vein in one arm for the collection of venous blood samples, and a venous catheter was placed in the contralateral median cubital vein for the drug or fluid administration. The lactated Ringer's solution 500ml was rapidly infused within 30 minutes before administration. All volunteers were supplied oxygen at flow rate of 10ml/min through the close fitting masks. Each volunteer was monitored HR, BP, SpO_2, ECG, end-tidal isoflurane concentration (ETiso) and temperature after at least 5 minutes of rest in supine position and all baseline values were obtained before administration.

After completion of the baseline data collection, emulsified isoflurane was infused at a rate of 0.4 ml/s using an electrical infusion pump via the catheter for fluid infusion. At the end of the infusion, the catheter was flushed with 1 ml normal saline. The lactated Ringer's solution was infused at 10 ml/kg/h within 1 h after administration. Vital signs were required closely monitored until 24 h after administration, and enough first-aid medicines and equipments were equipped to guarantee the safety of the volunteers.

ECG assessment

Standard 12-lead surface ECGs (paper speed of 50 mm/s) were collected using the MAC3500 Resting ECG Analysis System (GE Medical Systems, Milwaukee, WI, USA) before administration and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 19, 21, 23, 25, 27, 30, 35, 40, 45, 50, 55, 60 min after administration. The baseline QTc interval was calculated from the mean value of the 3 ECG recordings collected at 2, 4 and 6 min after the oxygen inhalation before administration. Any arrhythmia detected during the subsequent 60-minute monitoring was also recorded.

The QT and QTcB intervals were measured automatically by the MAC3500 Resting ECG Analysis System. The RR interval, which was not automatically measured on the ECG, was calculated from the automatically-measured QT and QTcB intervals, and then QTcF was obtained using the Fridericia's formula. When any interference occurred during the automatic ECG measurement, or the difference between the automatic value on the ECG and the manual read by the investigator was more than 20 ms, the manual measurement was performed by the same trained investigator. Among the 12 standard leads, lead II was selected as the most appropriate lead for the QT measurement (Booker, *et al*., 2003). The QT interval was measured manually using a caliper from the onset of the QRS complex to the end of the T wave, which was determined by the intersection of the tangent of the downward limb of the T wave and isoelectric line. When U wave appeared, the nadir where the T and U wave

intersected was regarded as the endpoint of the T wave. The end of biphasic T wave was considered as the final return to the baseline (Rautaharju *et al*., 2009). The QTcB change from the baseline (ΔQTcB) and the QTcF change from the baseline (ΔQTcF) were determined for each volunteer at each time point. The primary target variable was ΔQTcF.

Drug assay

The venous blood samples of 7 ml were collected from each volunteer at 0, 0.5, 1, 2, 3, 4, 5, 6, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 120 min after drug administration. The sample was immediately injected into a clear vial once collected from the vein and sealed with an aluminum cap. All of the samples were transported to the Laboratory of Anesthesia and Critical Care Medicine, Translational Neuroscience Center for drug assay. The plasma concentrations of isoflurane were measured using a gas chromatography (Agilent 4890D, Tegent Technology Ltd., Shanghai, China) equipped with a flame ionization detector. ET_{iso} were monitored by Patient Monitor (BeneView T8, Mindray, Shenzhen, China) before administration and once every 5 seconds after administration until the value was zero.

STATISTICAL ANALYSIS

According to the E14 guideline issued at ICH, the primary objective of the study in this article was to achieve a two-sided 90% confidence interval (90% CI) of the mean ΔQTcF in each group at each time point (the two-sided 90% CI equivalent to the one-sided 95% CI in the E14 guideline) (ICH, 2005; Vandemeulebroecke, *et al*., 2009). The upper limit of the 90% CI >10 ms with the lower limit >0 ms would suggest that intravenous emulsified isoflurane was associated with a QTc-prolonging effect.

The relationship between the drug dose and QTcF was evaluated by the Repeated Measures of General Linear Model followed by pot-hoc test. The comparison of QTcF among three dose groups at each timepoint was performed by one-way analysis of variance (one-way ANOVA). The relationships between QTcF and the plasma concentration of isoflurane (or ET_{iso}) were fitted using a linear regression.

All data were presented as mean ±SD or mean (90% CI). The statistical analyses were performed using PASW Statistics 18.0 (IBM, New York, US). A *P* value <0.05 was considered statistically significant.

RESULTS

Subjects

All of thirty subjects (15 men and 15 women) completed the study and were included for the analysis of the ECG data. No statistically significant difference was found among the three groups in the demographic data (table 1).

Effects of emulsified isoflurane on the QTc interval

All the QTcF values for all volunteers were <500 ms during the entire period, and the ΔQTcF >60 ms was observed in 1 female volunteer. The largest mean ΔQTcF was 11.9-29.2 ms, and the largest mean ΔQTcB was 35.8-46.7 ms.

In the study, the two-sided 90% CIs of the mean ΔQTcF at each time point were achieved. The QTc-prolongation effect of emulsified isoflurane occurred at 1, 6-8, 10-15, 21, 30 min for 22.63 mg/kg, 2, 4-60 min for 38.26 mg/kg, 4-40 min for 49.73mg/kg, respectively (fig. 1). The maximal two-sided 90% CIs of the mean ΔQTcF for 22.63, 38.26 and 49.73 mg/kg were 2.52-21.18 ms, 15.66-35.90ms and 17.65-40.71 ms, respectively.

The relationship between dose and the QTcF was evaluated by the Repeated Measures of General Linear Model followed by Post Hoc Tests. The results indicated that QTcF values for 22.63 mg/kg were statistically lower than 49.73 mg/kg (*P*=0.013), while there were no statistically significance between 38.26 mg/kg and 22.63 mg/kg (or 49.73 mg/kg) (P>0.05). The differences among three dose groups were statistically significant at 5-14, 17, 19, 27 min after administration (P<0.05) (fig. 2).

Pharmacokinetics

The pharmacokinetic profile of emulsified isoflurane for three doses (22.63, 38.26 and 49.73 mg/kg) is showed in fig. 3. The ET_{iso} result displayed rapid distribution of isoflurane in lungs and rapid exhalation of isoflurane from lungs (fig. 3a). The results of plasma concentration displayed rapid distribution and elimination of isoflurane in blood (fig. 3b). The maximal ETiso was 1.59-4.61%.

The time (median(range)to receive the maximal QTcF vs the time to receive the maximal plasma concentration was 7 (1-15) min vs 2 (1-5) min after administration (P< 0.05). The time (median (range)) to receive the maximal QTcF vs the time to receive the maximal ET_{iso} was 7 (1-15) min vs 0.96 (0.25-1.67) min after administration (P< 0.05). The results indicated that there was an apparent hysteresis between QTcF and the plasma concentration (or ET_{iso}).

Relationship between QTc interval and concentrations

The relationship between the QTcF and ETiso was explored in a linear regression model. The formula was the following:

$$QTcF = -2.120 \times ET_{iso} + 419.656$$

ET_{iso} was the end-tidal isoflurane concentration. The correlation coefficient was 0.054 (*P*=0.240, fig. 4a), which meant that there was no correlation between the QTcF and ETiso.

The relationship between the QTcF and the plasma concentration of isoflurane was also presented in fig. 4a

Table 1: Demographic characteristics

	22.63 mg/kg (n=10)	38.26 mg/kg (n=10)	49.73 mg/kg (n=10)	*P*
Age (years)	22.4±1.3	22.2±2.3	23.6±2.5	0.275
Height (cm)	166.5±7.0	167.4±9.9	164.1±7.1	0.645
Weight (kg)	58.1±6.4	59.6±7.2	58.6±6.6	0.889
BMI (kg/m^2)	20.93±1.55	21.21±1.44	21.72±1.53	0.501
QTcB (ms)	414±24	413±23	424±11	0.414
QTcF(ms)	400±19	405±17	413±12	0.224
HR (bpm)	75±9	67±9	72±11	0.249

Data are presented as the arithmetic mean (±SD); BMI: body mass index; Bpm: beats per minute.

Table 2: Number (%) and distribution of volunteers with abnormal findings in ECG assessment

ECG-related adverse events	Does group (mg/kg)			N (%) (n=30)
	22.63	38.26	49.73	
Sinus tachycardia	1	4	5	10(33.3)
T wave abnormality	2	3	3	8(26.7)
QTc prolongation	0	3	3	6(20.0)
Sinus bradycardia	0	1	1	2(6.7)
Abnormal ST segment	1	0	0	1(3.3)
Erratic rhythm from sinuatrial node to junctional area	0	1	0	1(3.3)
Erratic rhythm from sinuatrial node to inferior part of atrium	0	0	1	1(3.3)
Atrial tachycardia	0	0	1	1(3.3)
First degree atrioventricular block	0	0	1	1(3.3)

using a linear regression model. The formula was the following:

$$QTcF = 0.003 \times Concentration + 414.183$$

Concentration was the plasma concentration of isoflurane. The correlation coefficient was 0.003 (*P*=0.958, fig. 4b), which meant that there was no correlation between the QTcF and the plasma concentrations.

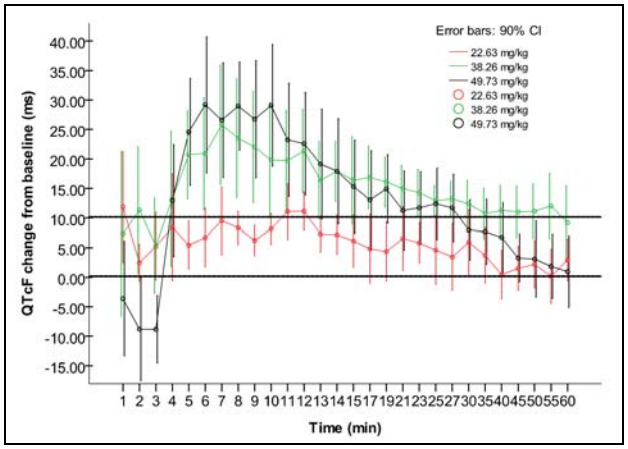

Fig. 1: QTcF change from baseline of an intravenous bolus injection of 22.63, 38.26, or 49.73 mg/kg emulsified isoflurane (n = 10 per dose).
Data are presented as the arithmetic mean and the two-sided 90% confidence interval (90% CI). The horizontal dashed lines respectively represent the upper limit of the two-sided 90% CI (10 ms) and the lower limit of the two-sided 90% CI (0 ms).

Safety Assessments

All adverse events (AEs) observed in ECGs were recorded in table 2 during the entire period. The most-frequently-experienced ECG-related AE was sinus tachycardia, followed by T-wave abnormality and the QTc prolongation (QTcF >450 ms for man; QTcF >470 ms for woman) (CPMP, 1997). All ECG-AEs were mild or moderate in severity without any clinical syndrome and disappeared at the end of the study.

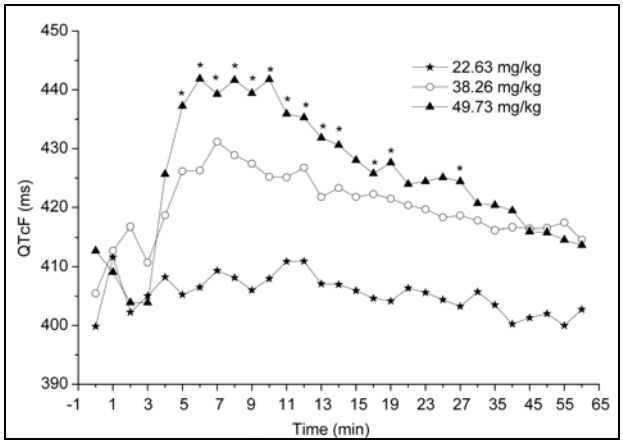

Fig. 2: Arithmetic mean QTcF interval vs. time profiles after an intravenous bolus injection of 22.63, 38.26, or 49.73mg/kg emulsified isoflurane (n=10 per dose).
*significant difference among three dose groups at each timepoint ($p<0.05$).

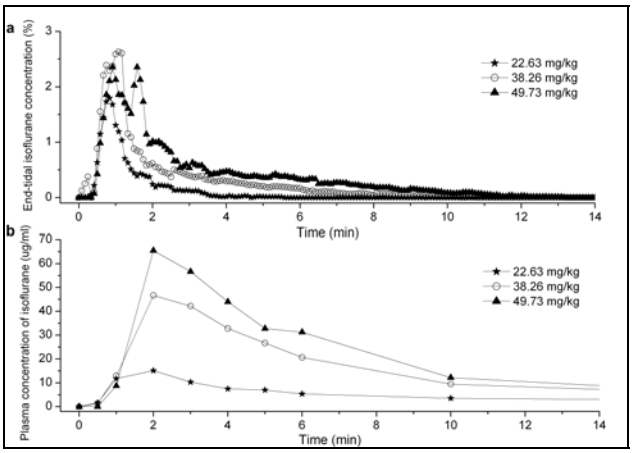

Fig. 3a: Arithmetic mean end-tidal isoflurane concentration vs. time profiles after an intravenous bolus injection of 22.63, 38.26, or 49.73 mg/kg emulsified isoflurane (n=10 per dose). **b**: Arithmetic mean plasma concentration of isoflurane vs. time profiles after an intravenous bolus injection of 22.63, 38.26, or 49.73 mg/kg emulsified isoflurane (n=10 per dose)

The most frequent drug-related adverse events after administration of emulsion isoflurane were injection site pain (73.3%) and apnea (73.3%), followed by bucking, involuntary movement, hypotension, hypertension, respiratory depression and dizziness. All drug-related adverse events were mild to moderate intensity. No serious adverse event (SAE) was reported in this study.

DISCUSSION

In a previous phase I tolerability study, 22.63mg/kg was considered as an anticipated therapeutic dose, so the anticipated therapeutic dose and supra-therapeutic doses (38.26 and 49.73mg/kg) were designed in this study. With a pharmacokinetic profile of rapid distribution and exhalation from lung, frequent ECGs obtained in the first 60 minutes after administration were enough to capture a peak QTc effect of emulsified isoflurane.

According to the E14 guideline, the primary objective of the study in this artical was to achieve the two-sided 90% CIs of the mean ΔQTcF at each time point. The upper limit of 90% CI >10 ms with the lower limit >0 ms would support that emulsified isoflurane was associated with a QTc-prolongation effect in healthy volunteers (Vandemeulebroecke, *et al*., 2009).

The relationship between dose and the QTcF indicated that single dose of emulsified isoflurane of 22.63, 38.26 or 49.73 mg/kg was associated with a potential dose-dependent QTc-prolongation effect. While there was no linear correlation between the QTcF and the plasma concentration of isoflurane (or ETiso). The most possible mechanism of the dose-depended and non-concentration-related QTc prolongation effect might be related two factors: one is the hysteresis between QTcF and the plasma concentration (or ET_{iso}), the other is the method of the linear regression. The cardiac muscle intook the drug slowly from the blood and the tissue fluid, so the time to receive the peak effect-site (cardiac muscle) concentration was later than the time to receive the peak plasma concentration (or the peak ET_{iso}). Then the QTc-prolongation effect lagged behind the plasma concentration (or ET_{iso}). The hysteresis between QTcF and the plasma concentration (or ET_{iso}) might interfer with the linear relationship between them, so there was not a concentration-related QTc prolongation effect.

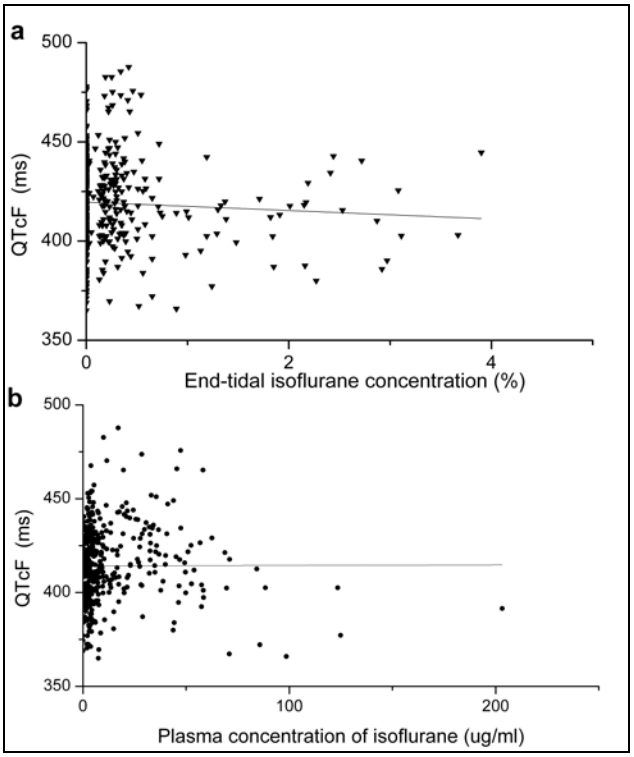

Fig. 4: a Scatter plot of QTcF vs. the end-tidal isoflurane concentration b Scatter plot of QTcF vs. the plasma concentration of isoflurane.

The results of the effects of emulsified isoflurane on the QTc interval came from a pharmacokinetics study without the recommended design of a thorough QT/QTc (TQT) study. So this study was a precursor to a large TQT study.

There is no consensus on the optimal choice of the QT correction method (Vandemeulebroecke, *et al*., 2009; Malik, *et al*., 2002). There is a great individual variability between the QT/QTc and RR interval, so various subject-specific or sex-specific corrections were used in some TQT studies and some corrections showed certain advantages (Vandemeulebroecke, *et al*., 2009; Malik, *et al*., 2002; Desai, *et al*., 2003). The baseline ECGs in this study were collected only at three time points (not in a whole baseline day) before administration. So a subject-

specific or sex-specific correction method was not used in this study because of the absence of enough baseline ECG data available. The weakness would decrease the confidence of the conclusion.

Because of the absence of placebo, the assessment of the effects of emulsified isoflurane on the QTc interval depended on the ΔQTc, not a baseline-adjusted, placebo-corrected QTc (ΔΔQTc) (Darpo, 2010). According to the definition of the TQT study, the conclusion might be less convincing. On the other hand, the absence of a positive control in this study failed to evaluate the required assay sensitivity according to the E14 guideline. The chance of a false-positive QTc-prolongation effect of emulsified isoflurane increased accordingly. Considering that this study was only a preliminary assessment on the QTc prolongation, the results were considered to be suggestive and inconclusive, and a false-positive QTc effect was more acceptable than a false-negative effect.

In clinical practice, there are several factors affect the effects of QT interval prolongation (Lindgren, *et al*., 1993). Drugs including anti-arrhythmics and non-anti-arrhythmics are one of the most important factors that cause the prolongation of the QT interval. Some drugs were withdrawn from the market or restricted to a second-line status because of the QT interval prolongation which may cause a fatal TdP (Roden, 2004; Haverkamp, *et al*., 2000; FDA, 2010). Previous studies showed that the mean QTcB interval was prolonged 20-50 ms from the baseline by the 1.1-3.5% steady ETiso, the similar degree as the largest mean ΔQTcB (35.8-46.7 ms) for the anticipated therapeutic dose or supra-therapeutic doses with the maximal ETiso (1.59-4.61%) in this study (Schmeling, *et al*., 1991; Yildirim, *et al*., 2004; Sun, *et al*., 2012; Guler, *et al*., 2001).

In this study, the QTcF values for all volunteers were <500 ms during the entire period, while ΔQTcF >60 ms was observed in 1 female volunteer. While QTc >500 ms or ΔQTc >60 ms are commonly used as thresholds for potential discontinuation of a study, the exact criteria chosen for a given trial will depend on the risk-tolerance level considered appropriate for the subjects. The QTc prolongation is commonly encountered under general anesthesia. In this study, none of the volunteers had a QTcF value >500 ms, and only a female volunteer experienced a ΔQTcF value >60 ms. The ΔQTcF decreased to <30 ms from 25 min after administration without any clinical symptom. In this study, the prolongation of QTc interval was self-limited, and the corresponding arrhythmia and clinical symptoms were not observed.

CONCLUSION

Single intravenous dose of emulsified isoflurane of the anticipated therapeutic dose or supra-therapeutic doses was associated with a potential dose-dependent and non-concentration-related QTc-prolongation effect.

No serious adverse event occured in this study and no volunteer discontinued because of adverse events. All drug-related adverse events were mild to moderate intensity. So In this study, emulsified isoflurane had a good safety in this study. Because this study was a preliminary assessment on the effects of emulsified isoflurane on the QTc interval in the healthy volunteers, a much larger trial would be necessary.

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