Modeling the Effect of Sevoflurane on Corrected QT Prolongation

A Pharmacodynamic Analysis

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ABSTRACT

Background: Sevoflurane may prolong the corrected QT (QTc) interval in healthy humans when administered for induction and maintenance of anesthesia. Little information is available about the dose-response relationship of sevoflurane on the QTc interval. We performed a pharmacodynamic analysis of the relationship between end-tidal sevoflurane concentration (C_{ET}) and the QTc.

Methods: Twenty-one patients aged 20–50 yr were enrolled in this study. Sevoflurane concentrations were progressively increased and then decreased over 15 min at the start of anesthesia; C_{ET} and automated QT interval were recorded continuously. Pharmacodynamic analysis using a sigmoid E_{max} model was performed to assess the concentration-effect relationship.

Results: Maximal C_{ET} was 4.30 ± 0.33%. Measured baseline and maximally prolonged QTc interval values were 351.7 ± 15.4 ms and 397.8 ± 17.5 ms, respectively. During sevoflurane anesthesia, increased concentrations were correlated with prolonged QTc interval. Hysteresis between the C_{ET} and QTc interval were observed and accounted for in the model. C_{e50} and k_{e0} were 2.5 ± 1.4 and 2.0 ± 1.0, respectively. The median prediction error, median absolute prediction error, and the co-efficient of determination (R^2) were 0.02%, 0.75%, and 0.95, respectively. The effect-site concentration (C_{e50}) and QTc interval data fit to a sigmoid E_{max} model.

Conclusions: Among patients receiving sevoflurane for anesthesia, QTc interval changes correlate to anesthetic level. The C_{e50} for significant QTc change is at clinically relevant levels of sevoflurane anesthesia.

What We Already Know about This Topic

❖ Sevoflurane may prolong the corrected QT (QTc) interval of the electrocardiogram in healthy patients.

❖ There is little information about the concentration-response relationship of the effect of sevoflurane on the QTc interval.

What This Article Tells Us That Is New

❖ The QTc interval changes produced by sevoflurane are concentration-related.

❖ The QTc interval is prolonged by clinically relevant sevoflurane concentrations.

THE QT interval represents the total duration between the onset of electrical depolarization of the ventricles and the end of repolarization. Prolongation of the QT interval is an alteration of the electrocardiogram that may result in potentially dangerous ventricular arrhythmias including tachycardia, fibrillation, and asystole, resulting in syncope, seizure-like episodes, and sudden cardiac death.[1–4] Long QT syndrome may result from exposure to various factors including anesthetic drugs and cardiac, neurologic, and electrolyte disturbances as well as congenital mutation of cardiac ion channels.[5,6]

Sevoflurane is a popular volatile anesthetic because of its low blood-gas solubility, which leads to rapid induction and emergence from anesthesia. In some electrocardiogram studies, it was shown that sevoflurane prolonged the corrected

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QT (QTc) interval during induction of inhalational anesthesia.[7–10] However, there is little published information in the literature specifying the dose-effect relationship of sevoflurane on the QTc interval.[11,12] Pharmacodynamic modeling can be useful in describing this relationship. The main objective of this study was to examine the relationship between end-tidal sevoflurane concentration (C_{ET}) and QTc interval prolongation during the onset of inhalational anesthesia in healthy adults.

Materials and Methods

Patients and Anesthesia

After obtaining approval from the institutional review board at Yonsei University College of Medicine (Seoul, Korea) and written informed consent from participants, 21 patients (American Society of Anesthesiologists Physical Status Classification P1 or P2) aged 20–50 yr were enrolled in this study. Patient exclusion criteria were: abnormal serum electrolyte values, a QTc interval duration greater than 440 ms, concomitant medication known to affect QTc interval duration (*e.g.*, tricylic antidepressant agents, antidysrhythmics, β-adrenergic antagonists, calcium channel blocking agents), existence of valvular cardiac disease, any cardiac rhythm other than sinus rhythm, diabetes mellitus, pregnancy, or obesity.

All study data were collected in the morning (8:00–10:00 AM) to restrict the effects of day-night changes on the QTc interval. Patients received no premedication. After patients were taken into the operating room, electrocardiogram monitoring, pulse oximetry, noninvasive blood pressure, and fraction of inspired oxygen with C_{ET} and carbon dioxide concentration monitoring were begun. Blood pressure was measured with an automatic oscillographic device every 2 min during the study period. After the monitoring equipment was attached, patients were allowed to rest for 5 min while lactated Ringer's solution, 4 ml/kg, was infused before inducing anesthesia. A standard real-time automated three-lead electrocardiogram was continuously recorded using a data acquisition system (PowerLab; AD Instruments, Colorado Springs, CO). The QT interval was measured in lead II from the onset of the QRS complex to the end of the T wave, defined as a return to the TP baseline. When U waves were present, the nadir between the T and U waves was regarded as the end of the QT interval. Biphasic T waves were considered finished with the final return to baseline. The values of the QT interval of four successive beats were averaged. The QT interval was corrected using the Fridericia formula: QTc = QT/$\sqrt[3]{(R - R \text{ interval})}$.[13]

Study Measurements

Anesthesia was induced by sevoflurane inhalation only with a tight-fitting facemask and 6 l/min airflow of 100% oxygen. The sevoflurane vaporizer was initially set at 1% and was increased stepwise 1% each minute, up to a maximum vaporizer setting of 8%. Subsequently, the vaporizer was de-

creased stepwise 1% each minute until sevoflurane was returned to 1%. As spontaneous breathing diminished, patients were manually assisted *via* facemask while an exhaled tidal volume of 8 ml/kg was maintained. Respiratory rate was adjusted to maintain an end-tidal carbon dioxide partial pressure of 35 mmHg. No other drugs were administered and the patients were left unstimulated during the study period. After the measurements were completed, anesthesia was continued according to the individual needs of the patient and type of surgical intervention: opioids, muscle relaxants, tracheal intubation, or laryngeal mask airway, as required.

Data Analysis and Model Selection

C_{ET} and corresponding QTc interval data along with demographic information were used to develop a pharmacodynamic model using NONMEM (nonlinear mixed effects modeling) software (version VII; GloboMax, Hanover, MD). The model provides estimates of the population mean parameters, interindividual, and residual random effects. The pharmacodynamic model was run using the first-order conditional estimation method with interindividual-residual interaction to determine parameter estimates. To account for the delay between C_{ET} measurements and the drug concentration at the site of drug effect, an effect compartment (C_e) was modeled. It was assumed that C_{ET} was linearly linked to C_e, which was estimated with the use of the following equation. dC_e/dt = $(C_{ET} - C_e) \times k_{e0}$, where k_{e0} is the first-order rate constant determining the equilibration between the two. The C_e over time was calculated as the convolution of the end-tidal concentrations over time with the disposition function of the effect site. The convolution was based on a "connect-the-dots" approach, previously used by Schnider *et al.*[14] The k_{e0} was estimated by minimizing the area of the hysteresis loop of QTc data *versus* C_{ET}. One individual k_{e0} value was calculated for each patient on the basis of his or her particular inhalation anesthetic ramp. The relationship between C_e and QTc interval was modeled using a sigmoid E_{max} model: $E = E_0 + (E_{max} - E_0) \times C_e^\lambda/(C_{e50}^\lambda + C_e^\lambda)$, where E_0 is the baseline QTc interval in the absence of sevoflurane, E_{max} is the maximum increase in the QTc interval, C_{e50} is the effect-site sevoflurane concentration required to achieve 50% of the maximum increase in the QTc interval, and λ is the steepness of the concentration-response relation curve.

Interindividual variability in E_0, E_{max}, C_{e50}, λ, and k_{e0} was modeled using an exponential error model. Residual intraindividual variability was modeled using additive error model. In our modeling approach, we first developed the base population model without covariates included. Then, we explored additional covariates of sex, age, height, and weight successively to determine their impact on estimates of the model parameters.

Statistical Analysis

For model assessment, the minimum value of the objective function was considered together with the model parameter

Table 1. Patient Characteristics (N = 21)

Characteristic	Mean ± SD	Range
Sex		
Men, no.	9	—
Women, no.	12	—
Age, yr	37.1 ± 8.6	21–49
Weight, kg	61.0 ± 8.1	52–78
Height, cm	163.7 ± 7.7	150–178

estimates, median prediction error, median absolute prediction error, and the coefficient of determination (R^2). For each analysis, NONMEM computed the minimum value of the objective function, a statistic that is proportional to minus twice the log likelihood of the data. Covariates were

added using a forward addition/backward substitution approach. A covariate was considered significant when its inclusion lowered the minimum value of the objective function by at least 3.85 points. The difference in minimum value of the objective function between two nested models in approximately chi-square distribution and can be used for significance tests ($P < 0.05$, with 1 degree of freedom). Data are presented as mean ± SD.

Results

Twenty-one patients completed the study (table 1). Adequate airway management was obtained in all patients without requiring insertion of an oral airway. Peripheral oxygen saturation was maintained above 95% throughout the study
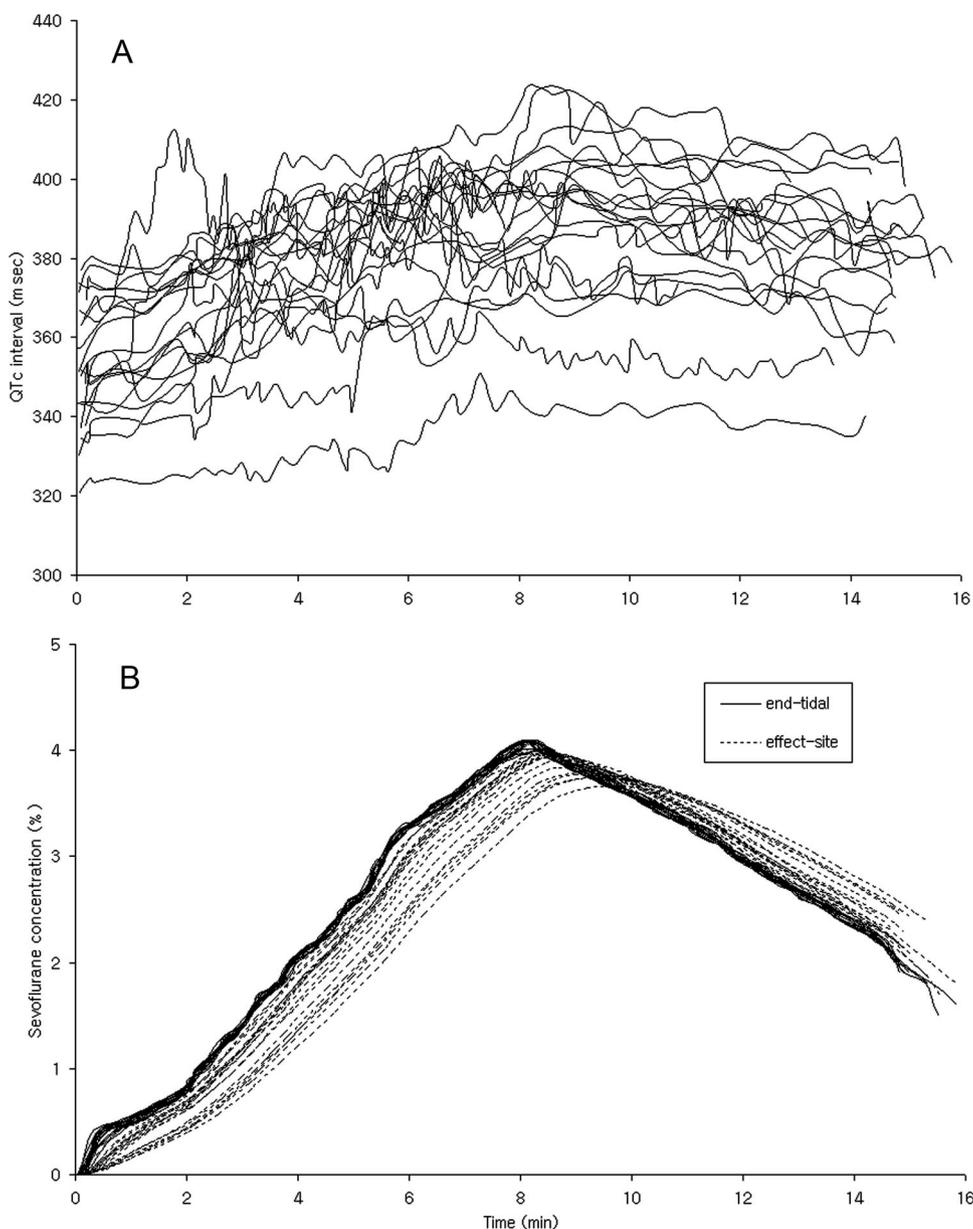
Fig. 1. The time course of the measured QTc interval change (*A*) and of the sevoflurane end-tidal and estimated effect-site concentrations (*B*) in all patients. QTc interval = corrected QT interval.
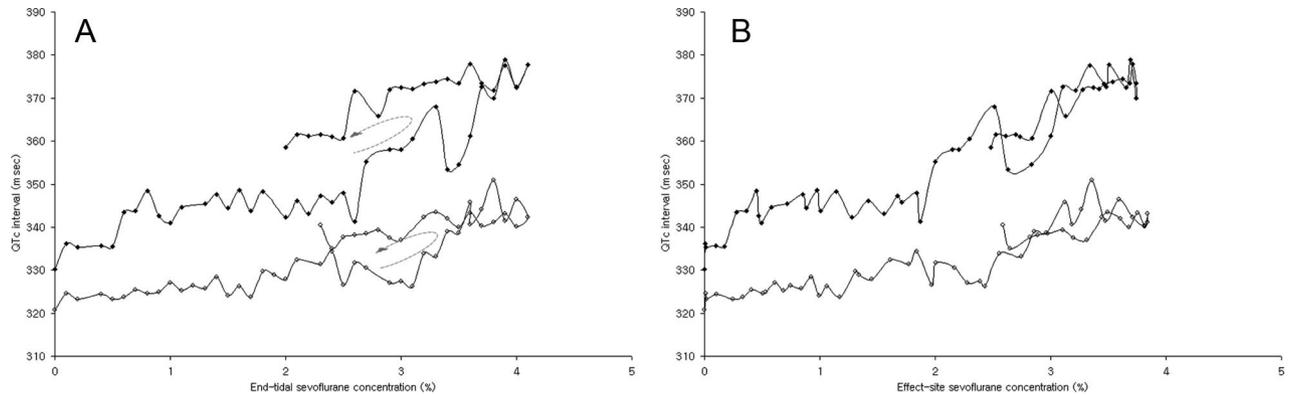
Fig. 2. The relationship between QTc interval and the end-tidal sevoflurane concentration (*A*) and effect-site sevoflurane concentration (*B*) for two representative patients. The *gray dotted arrows* indicate the counter-clockwise hysteresis. QTc interval = corrected QT interval.

period in all patients. Maximal C_{ET} was 4.30 ± 0.33%. Among the total 5,347 measurements of QTc interval, the measurements that were made for the 15 s before changing the C_{ET} were used for modeling the concentration-QTc relationship. It was anticipated that these 1,220 measurements were more closely equilibrated to the C_{e50}.

Mean baseline QTc interval values were 351.7 ± 15.4 ms, with values ranging from 320.8–377.2 ms and showing a relatively wide dispersion. The mean maximally prolonged QTc interval value observed during the study period was 397.8 ± 17.5 ms. All patients maintained a normal sinus rhythm during the study despite the prolonged QTc interval.

Figure 1 shows the time course of the C_{ET} and changes in QTc interval in all patients where increased concentrations were correlated with prolongation of QTc interval. Two patients showed the maximal prolongation of QTc interval at approximately 1% sevoflurane concentration after which their QTc interval decreased slightly despite increasing sevoflurane concentration. Data from those two patients were excluded from concentration effect modeling to improve the stability of the pharmacodynamic model. For the remaining 19 patients, plotting C_{ET} *versus* QTc interval in time order revealed counterclockwise hysteresis (fig. 2A), which collapsed by introduction of C_{e50} (fig. 2B). The rela-

tionship between the observed and the *post hoc* Bayesian predicted QTc interval *versus* C_{e50} is plotted in figure 3. For these 19 subjects, the QTc interval increased with increasing C_e and a sigmoid E_{max} model could be fitted to the data. The predicted QTc interval calculated using the parameters derived from the sigmoid E_{max} model was plotted against the measured QTc interval for comparison (fig. 4).

The mean ± SD estimates of all parameters for the sigmoid E_{max} model are summarized in table 2. The C_{e50} and k_{e0} were 2.5 ± 1.4% and 2.0 ± 1.0 min^{-1}, respectively. The residual variability (residual error σ) for sigmoid E_{max} model was 4.5. The median prediction error, median absolute prediction error, and R^2 were 0.02%, 0.75%, and 0.95, respectively. Demographic variables did not influence the parameters in the model for the analyzed subjects.

Sevoflurane administration did not significantly alter the heart rate. Sevoflurane produced a concentration-dependent reduction of mean arterial pressure. The lowest mean arterial pressure values recorded in each patient were 67.8 ± 9.4 mmHg.

Discussion

This was the first study to apply a pharmacodynamic model to quantitatively describe the effect of sevoflurane on QTc
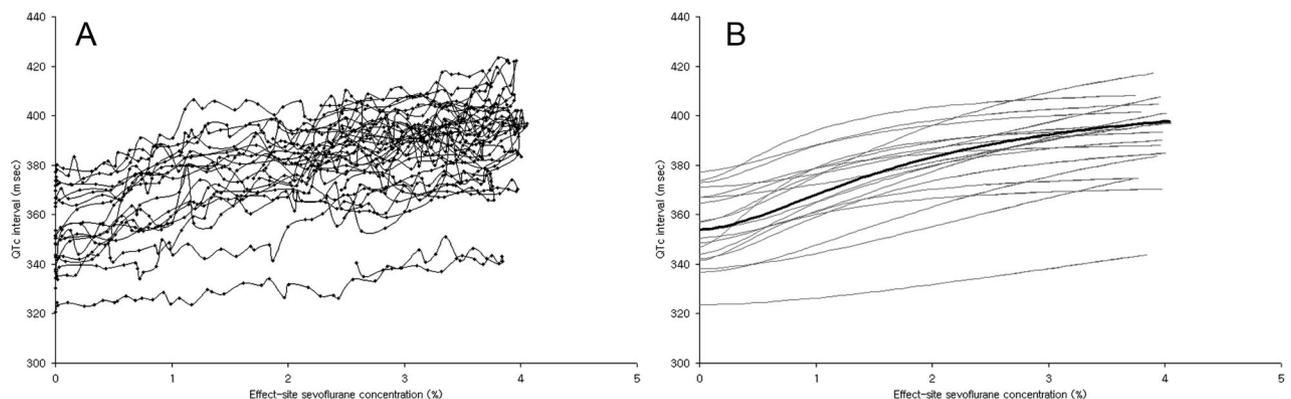
Fig. 3. (*A*) Observed raw QTc interval *versus* the calculated sevoflurane effect-site concentration. (*B*) The *thin gray lines* represent individual predicted values of QTc interval, whereas the *bold black line* represents the typical curve of the population data. QTc interval = corrected QT interval.
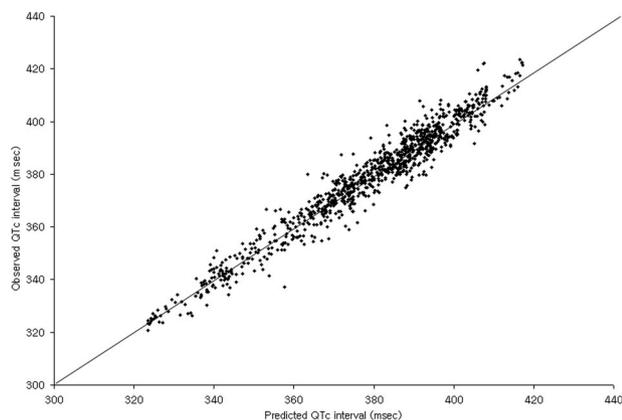
Fig. 4. The relationship between the observed and individual predicted values of QTc interval. The *solid line* represents the line of identity. QTc interval = corrected QT interval.

interval. Increasing sevoflurane concentration had a pronounced effect on QTc interval in 19 of 21 subjects, prolonging it by up to an average maximal value of 46 ms. This result corresponds to a maximum increase of around 13% compared with the baseline QTc interval. The extent of sevoflurane-associated QTc prolongation might be of clinical significance for patients presenting with the long QT syndrome, hypokalemia, or in presence of other drugs or factors that lengthen QTc.[2,15] Among patients presenting with a prolonged QTc interval, the choice of sevoflurane may be considered with caution.

There are few publications in the literature in which sevoflurane dose or end-tidal concentration *versus* QT interval response was investigated, making it unclear whether sevoflurane prolongs QTc interval in a dose-dependent manner.[11,12] It is probably difficult to determine the effects of individual anesthetic agents because most of the drugs in clinical anesthetic practice may interfere with the duration of the QTc interval. Whyte *et al.*[12] suggested that sevoflurane non–dose dependently prolonged the QTc interval in healthy children, whereas sevoflurane (1–4%) prolonged QTc in a dose-dependent manner in guinea pigs as reported by Yamada *et al.*[11] It is not easy to explain the discrepancies between these studies, but it is likely that the

Table 2. Pharmacodynamic Model Parameters: Effect of Sevoflurane on Corrected QT Prolongation

Parameter	Mean ± SD
E_0, ms	354.6 ± 15.2
E_{max}, ms	412.5 ± 27.2
C_{e50}, %	2.5 ± 1.4
λ	2.0 ± 0.8
k_{e0}, min^{-1}	2.0 ± 1.0

C_{e50} = effect-site sevoflurane concentration required to achieve 50% of maximum increase in the corrected QT interval; E_0 = baseline corrected QT interval in absence of sevoflurane; E_{max} = maximum increase in corrected QT interval; k_{e0} = first-order rate constant determining the efflux from the effect-site; λ = slope of sigmoid relation between sevoflurane end-tidal concentration and effect.

result of the former study might be attributed to an insufficient number of subjects and the use of a relatively short range of sevoflurane concentrations (0.010–0.015 minimum alveolar concentration).[12]

The experimental design in this study was chosen to allow enough time at a particular C_{ET} for the effect-site to approach equilibration. Given that the average effect-site time constant was 2.0 min^{-1}, which would equate to an effect-site half-life of 0.35 min, the experiment design represents a reasonable compromise that allows for the accurate assessment of the effect but still provides an anesthetic induction that is typical of daily clinical practice. The effect-site compartment, estimated from the hysteresis observed by plotting C_{ET} *versus* QTc interval, allowed us to estimate C_{e50} and account for the delay in onset and offset of effect. This method allows the QTc effect to be studied during non–steady state conditions and provides an estimate of the equilibration rate between C_{ET}, a variable that is clinically available, and the blood-myocardium equilibration time.[16] The mean value of QTc k_{e0} in our data (2.0 min^{-1}) was faster than the k_{e0} of processed electroencephalogram, representing the main anesthetic effect of sevoflurane on the central nervous system.[17–20] Our results suggest that the QTc interval reacted faster to changes in sevoflurane concentration than the processed electroencephalogram would. This difference is probably explained by more rapid equilibration between blood and myocardium than between blood and brain.

The values of E_0 and E_{max} had high interindividual variability. This variability could be due to the different baseline values of QTc interval by sex.[21] Both raw QTc values of baseline (355.1 ± 14.3 ms) and maximal (403.3 ± 13.4 ms) prolongation in women were greater than those observed in men (346.0 ± 16.5 ms and 388.9 ± 20.4 ms, respectively) (data not shown). Unfortunately, sex as a covariate did not significantly improve the model fit to the data. The reason for this lack of effect is unclear, but it could be due to a study design that uses a relatively small patient cohort. According to the pharmacodynamic modeling, half of the maximal change in QTc interval, 29.0 ms, could result from a C_{e50} value of 2.5%. Our findings are comparable with those of other studies, which showed 22–26-ms changes in QTc interval with steady state levels of 2.0–2.5% sevoflurane anesthesia.[7,8,10]

The predicted mean values of E_{max} and C_{e50} should be considered with caution. Some patient data showed that the predicted QTc interval *versus* effect-site sevoflurane concentration curve did not plateau to the maximum effect at concentrations within the range of the current data. Therefore, this estimate of the E_{max} was an indirect measure dependent on the curvature present in the available data rather than a direct measure of an actual plateau in all the data. The predicted mean value of C_{e50} was consequently larger than anticipated from review of the raw data.

The two patients whose data were excluded when building our model showed sudden increased heart rates at the early phase of increasing sevoflurane concentration, which

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altered the ability to determine changes in QTc. The absence of premedication may have produced anxiety, which might manifest as tachycardia.[22] Several stimuli leading to sympathetic stimulation, such as anxiety, emotional stress, physical stress, and loud auditory stimulation, may prolong QTc intervals.[15,23] Hence the use of premedication for preventing the release of catecholamine may be helpful for patients with QTc prolongation. To avoid the confounding effects of other agents in our analysis, the patients in this study received no premedication.

The Bazett correction is the method most commonly employed to correct the QT interval for changes in heart rate in clinical electrocardiogram practice. However, this method is known to overcorrect the QT interval for fast heart rate and undercorrect it for slow heart rate—potentially leading to false diagnosis of QTc interval, especially given that heart rate can be extremely dynamic during general anesthesia.[24] The fixed exponent Fridericia correction is considered a much better approach,[25] although there is no standard method of heart rate correction in the QTc interval.[25–27]

We conclude that QTc interval changes correlate to sevoflurane concentration and are significant at clinically relevant concentrations. The concentration-response curves could be adequately described with a sigmoid E_{max} model, using effect compartment concentrations rather than C_{ET} as independent variable. Despite the absence of cardiac arrhythmias, patients with congenital or acquired prolonged QTc interval might need to be monitored closely at clinically relevant levels of sevoflurane anesthesia.

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