Anesthesiology 2003; 98:639–42

Sustained Prolongation of the QTc Interval after Anesthesia with Sevoflurane in Infants during the First 6 Months of Life

Alex Loeckinger, M.D., Axel Kleinsasser, M.D.,† Stephan Maier, M.D.,‡ Bernhard Furtner, M.D.,‡ Christian Keller, M.D.,§ Gabriele Kuehbacher, M.D.,§ Karl H. Lindner, M.D.‖*

Background: **Sevoflurane, an inhalational anesthetic frequently administered to infants, prolongs the QT interval of the electrocardiogram in adults. A long QT interval resulting in fatal arrhythmia may also be responsible for some cases of sudden death in infants. As the QT interval increases during the second month of life and returns to the values recorded at birth by the sixth month, we evaluated the effect of sevoflurane on the QT interval during and after anesthesia in this particular population.**

Methods: **In this prospective two-group trial we examined pre-, peri-, and postoperative electrocardiograms of 36 infants aged 1 to 6 months scheduled for elective inguinal or umbilical hernia repair. Anesthesia was induced and maintained with either sevoflurane, or the well-established pediatric anesthetic halothane. Heart rate corrected (c) QTc and JTc interval (indicator of intraventricular conduction delays) were recorded from electrocardiograms before and during anesthesia, and at 60 min after emergence from anesthesia.**

Results: **Prolonged QTc was observed during sevoflurane anesthesia (mean [±SD], 473 ± 19 ms, $P < 0.01$). Sixty minutes after emergence from anesthesia, QTc was still prolonged (433 ± 15 ms) in infants treated with sevoflurane compared with those treated with halothane (407 ± 33 ms, $P < 0.01$). Analogous differences were found for the JTc interval.**

Conclusions: **Despite a shorter elimination time than better known inhalational anesthetics, sevoflurane induction and anesthesia results in sustained prolongations of QTc and JTc interval in infants in the first 6 months of life. Electrocardiogram monitoring until the QTc interval has returned to preanesthetic values may increase safety after sevoflurane anesthesia.**

IN the United States, nationwide public education to avoid the prone position for infants resulted in a significant reduction in the incidence of sudden death in infants.[1,2,3] It has been suggested that long QT-syndromes may, among other factors, be responsible for some cases of sudden infant deat syndrome (SIDS).[4] Using an electrocardiographic assessment of 33,034 infants, Schwartz *et al*.[5] linked rate-corrected QT interval (QTc) of 440 ms or longer to death in infants, showing that 12 of 24 infants who had died had presented with a prolonged QTc interval at the initial electrocardiogram. Even though this finding has been vigorously discussed since, the case of cardiac arrest in an infant with sodium channel gene mutation confirmed evidence for the association between long QT and sudden death in infants.[6] Ackerman *et al*. recently reported a postmortem analysis of 93 cases of sudden death in infants where two cases had a mutated gene coding for a cardiac ion channel responsible for the QT interval duration.[7]

Drugs may also alter the QT duration, but there is no evidence yet that such drug effects on cardiac repolarization may be linked to sudden death in infants. Anesthesia with sevoflurane however, is known to prolong the QTc interval in adults,[8,9,10] and there is little information on the effect of sevoflurane on cardiac repolarization in infants.

Currently, sevoflurane is replacing halothane in pediatric anesthesia because it allows rapid induction *via* facemask. As the QTc interval increases during the second month of life and returns to the values recorded at birth by the sixth month,[11] we evaluated the effect of sevoflurane on cardiac repolarization in this particular cohort. We hypothesized that sevoflurane induction and anesthesia modifies cardiac repolarization in infants in the first 6 months of life.

Methods

Study Population

After approval by the institutional ethics committee of the Leopold-Franzens University, Innsbruck, Austria, and after written informed consent was obtained from the parents, this study was performed on 36 healthy infants scheduled for elective inguinal or umbilical hernia repair. Inclusion criteria were normal cardiovascular and pulmonary status, and hematologic status within the normal range. Preterm birth, apparent infection, or congenital heart defects led to patient exclusion.

Study Protocol

Infants were randomly assigned into two groups, one receiving sevoflurane induction and anesthesia, the other receiving halothane. Except for fentanyl (discussed later in the article) no other drug was administered throughout the study period. Before induction, a baseline electrocardiogram was recorded. Induction was performed by inhalation using an inspiratory percentage of five volume percent (vol%) sevoflurane or two vol% halothane, respectively *via* a facemask. Ventilation was first assisted, and later manually controlled to achieve an end-tidal P_{CO_2} of 40 Torr. End-tidal concentration was

* Assistant Professor, ‡ Research Resident, § Consultant, ‖ Chief of Department, Department of Anesthesiology and Critical Care Medicine, The Leopold-Franzens University. † Research Associate, Department of Medicine, Division of Physiology, University of California, La Jolla, California.

Received from The Leopold-Franzens University, Innsbruck, Austria. Submitted for publication June 21, 2002. Accepted for publication October 28, 2002. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Loeckinger: Department of Anesthesiology and Critical Care Medicine, The Leopold-Franzens University, 6020 Innsbruck, Austria. Address electronic mail to: alex.loeckinger@uibk.ac.at.

measured at the facemask. Airway management was exclusively performed using a facemask. Vaporizers were then adjusted to achieve end-tidal concentrations of 2.0 vol% sevoflurane (one minimum alveolar concentration [MAC]) or 0.8 vol% halothane (one MAC) in oxygen-enriched air. Fresh gas flow was set to 4 l/min. Fifteen minutes after induction, a second electrocardiogram was recorded. Fentanyl (0.005 mg/kg intravenously) was then routinely administered, and surgery was performed as scheduled. After completion of the procedure, anesthesia was stopped. A third measurement was taken 60 min after emergence, when a 1-ml blood sample was also taken for evaluation of plasma electrolytes, as these may alter cellular repolarization.

Electrocardiography

A standard three-lead electrocardiogram was used. Electrocardiograms were recorded at a paper speed of 50 mm/s. Measurements were made using lead II. QT and JT intervals were measured and calculated by two of the investigators who were blinded regarding gender, time point, and anesthetic. Calculations and measurements were then averaged. QTc was calculated using Bassett's formula ($QTc = QT/\sqrt{RR}$). JT interval, reflecting the phase from the end of the electrocardiographic ventricular wave complex to the end of the T wave, was measured to evaluate intraventricular repolarization delays.[12,13] Bazett's formula was used for rate correction.

Statistical Analysis

Sample size was selected to detect a projected difference of 10% between the two anesthetic groups with respect to the QTc (milliseconds) for a type I error of 0.05 and a power of 0.9. The power analysis was based on data from a previous study of 30 adult women in which QTc was measured during sevoflurane and propofol anesthesia. The distribution of data were determined using Kolmogorov-Smirnov analysis.

Differences between groups were examined using analyses of variance. Significant differences were *post hoc* analyzed using the Newman-Keuls test. Data are presented as mean ± SD. A P value of less than 0.05 was considered significant.

Results

Results are shown in tables 1 and 2 and in figure 1. Demographic data were comparable between groups. The 36 infants were 68 ± 37 *versus* 73 ± 32 days of age, weighing 5.0 ± 1.3 *versus* 5.4 ± 1.4 kg. Twenty-one male and fifteen female infants were examined.

Exposure time to either sevoflurane or halothane was comparable at 45 ± 9 *versus* 47 ± 9 min, respectively. Sevoflurane but not halothane induction and anesthesia resulted in a prolonged QT ($P < 0.01$) in intra- and in intergroup (table 1) comparisons and QTc ($P < 0.01$) (fig. 1) interval during and 60 min after emergence of anesthesia. Sevoflurane prolonged QTc to abnormally long levels during surgery (that is greater than normal of 440 ms) but postoperatively; QTc was not prolonged to Long QT Syndrome (LQTS) concentrations with either drug. Alterations analogous to those of QT and QTc were found examining the JT and JTc intervals ($P < 0.01$). Plasma concentrations of potassium, sodium, magnesium, and calcium were within the normal range in all infants examined (table 2).

Table 1. Heart Rate, QT, JT, and JTc Measurements

	Before Anesthesia	During Anesthesia	1 Hour after Anesthesia
Heart rate			
Sevoflurane	163 ± 22	148 ± 13	146 ± 21
Halothane	153 ± 21	141 ± 16	151 ± 16
QT, ms			
Sevoflurane	250 ± 23	301 ± 19*	278 ± 22*
Halothane	260 ± 20	273 ± 22	257 ± 22
JT, ms			
Sevoflurane	206 ± 20	256 ± 16*	233 ± 19*
Halothane	215 ± 17	227 ± 20	212 ± 22
JTc, ms			
Sevoflurane	338 ± 21	403 ± 18*	363 ± 14*
Halothane	345 ± 21	347 ± 19	336 ± 34

Values are mean ± SD.

* $P < 0.01$ in intergroup comparison.

QT = the interval from the beginning of the Q wave to the end of the T wave; JT = the JT interval, reflecting the phase from the end of the electrocardiographic ventricular wave complex to the end of the T wave; JTc = heart rate corrected JT interval.

Discussion

This study evaluated the effects of sevoflurane and halothane on cardiac repolarization during and after anesthesia was administered to infants up to 6 months old. Sevoflurane resulted in significantly longer QTc and JTc intervals than halothane during and 60 min after emergence from anesthesia.

Pharmacokinetic Paradox

The question arises, why the QTc interval did not return to the baseline value after discontinuation of

Table 2. Surgery Performed and Plasma Electrolytes

	Infants Treated with Sevoflurane	Infants Treated with Halothane
Surgery		
Umbilical hernia	4	7
Inguinal hernia	14	11
Plasma electroytes		
Potassium	4.3 ± 0.3	4.2 ± 0.2
Sodium	139 ± 2	140 ± 2
Magnesium	0.73 ± 0.06	0.75 ± 0.08
Calcium	2.3 ± 0.2	2.4 ± 0.3

Plasma electrolyte concentrations were measured 1 hr after anesthesia. Values are given in mM.

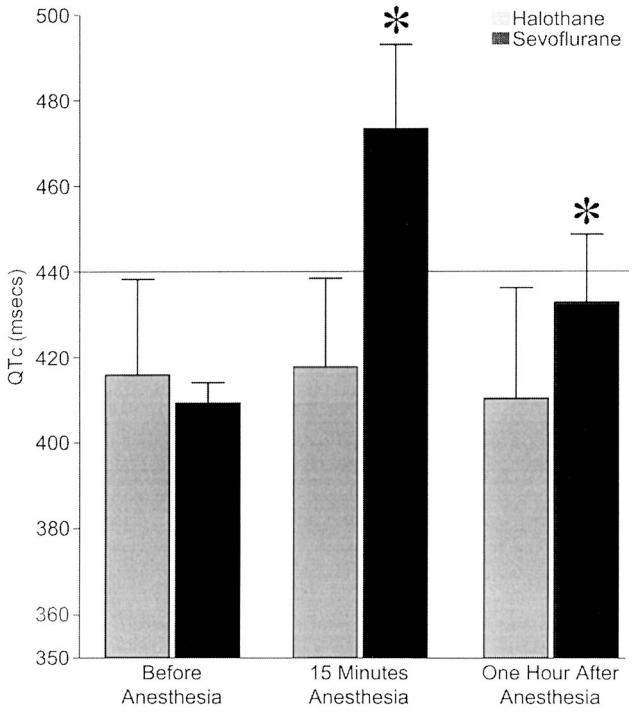

Fig. 1. QTc Amplitude. QTc before, during, and 1 h after anesthesia with sevoflurane or halothane assessed in 36 infants. The horizontal line at 440 ms reflects the critical upper value for QTc. *$P < 0.01$ in intergroup comparison.

sevoflurane. A sustained modification of the electrocardiogram was not anticipated, as sevoflurane has a very low blood gas partition coefficient (0.69) indicating very low solubility in blood. This particular physical property makes sevoflurane one of the fastest inhalational anesthetics available, allowing rapid induction and emergence of anesthesia. It is thus remarkable that the effects of sevoflurane on the QTc interval were still present 60 min after emergence from anesthesia.

Possible Mechanism of Prolongation

The mechanism of the observed phenomenon remains uncertain. How anesthetic vapors affect cellular membranes, receptors, and ion channels is not known. Long QT syndromes however, are now considered as cardiac channelopathies, and defects in, or blockade of, potassium channels may be responsible for drug-induced long QT syndromes.[14] Particularly the inner structure of the *KCNH2* potassium channel renders it susceptible for small organic molecules,[14,15] and channel blockade may lead to QT interval prolongation. Although the exact principle of action of anesthetic vapors on the cellular membrane and its substructures remains elusive, transitory or partial blockade of ion channels by anesthetic vapors may be a viable hypothesis.

Sevoflurane and Arrhythmia

Because sevoflurane is known to prolong the QTc interval in adults,[8,9,10] prolongation in infants was not surprising. Although it has not conclusively been shown, there is evidence that sevoflurane anesthesia may trigger ventricular fibrillation.[16] Undeniably, prolongation of the QT interval may lead to fatal tachyarrythmia,[17] which in turn has been proposed as a possible mechanism for SIDS.[5] Arrhythmia however, was not recorded in any of the infants examined.

The Endpoint Problem

Thirty-six infants were examined before, during, and 1 h after anesthesia. We learned that QTc was still prolonged at 1 h after anesthesia. To show that a sevoflurane-associated long QTc does return to normal, we examined three more infants at 3 h after anesthesia. In these three infants, QTc was insignificantly different to the baseline value. A graph of QTc values in these three infants is shown in figure 2.

Clinical Implications

Although electrocardiogram monitoring during anesthesia is already part of routine care, postoperative electrocardiogram modifications in infants up to 6 months old may possibly influence postoperative care. Criteria of discharge from the postanesthetic care unit may need to include the recording of a normal QTc interval. By the same token, sevoflurane may not be the drug of choice in infants with an already prolonged QT interval.

On the other hand, it should be noted that to our knowledge there is currently no report available that attributes an

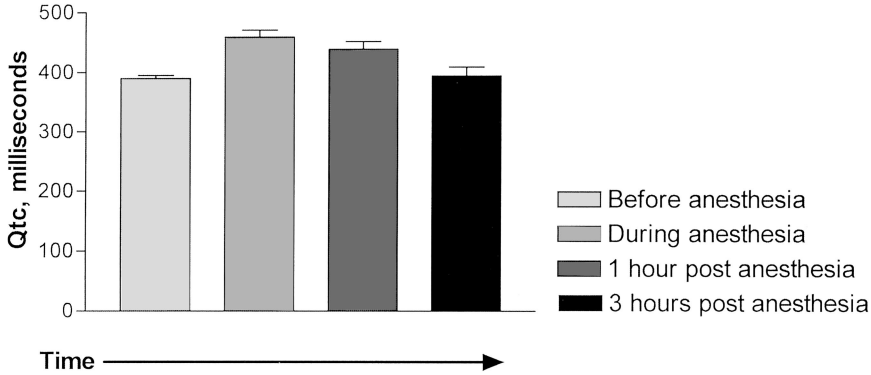

Fig. 2. Postoperative QTc Normalization. QTc in three infants before, during, and 1 and 3 h after sevoflurane anesthesia.

intraoperative or postoperative complication to cardiac repolarization abnormalities after sevoflurane.

Conclusion

We conclude that sevoflurane prolongs the QT(c) and JT(c) intervals during anesthesia and that prolongation is still present 60 min after emergence from anesthesia, in comparison to halothane anesthesia. Does electrocardiogram monitoring until the QTc interval has returned to preanesthetic values increase safety after sevoflurane anesthesia? A single measurement before discharge from the postoperative care unit to detect those with a long QTc may be a practicable alternative. However, further studies in larger groups of patients are warranted.

References

1. Paris CA, Remler R, Daling JR: Risk factors for sudden infant death syndrome: changes associated with sleep position recommendations. J Pediatr 2001; 139:771–7

2. American Academy of Pediatrics AAP Task Force on Infant Positioning and SIDS: Positioning and SIDS. Pediatrics 1992; 89:1120–6

3. Willinger M, Hoffman HJ, Hartford RB: Infant sleep position and risk for sudden infant death syndrome. Pediatrics 1994; 93:814–9

4. Antzelevitch C: Molecular biology and cellular mechanisms of Brugada and long QT syndromes in infants and young children. J Electrocardiol 2001; 34: 177–81

5. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticone F, Rosti D, Salice P: Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998; 338:1709–14

6. Wedekind H, Smits JP, Schulze-Bahr E, Arnold R, Veldkamp MW, Bajanowski T, Borggrefe M, Brinkmann B, Warnecke I, Funke H, Bhuiyan ZA, Wilde AA, Breithardt G, Haverkamp W: De novo mutation in the SCN5A gene associated with early onset of sudden infant death. Circulation 2001; 104:1158–64

7. Ackerman MJ, Siu BL, Sturner WQ, Tester DJ, Valdivia CR, Makielski JC, Towbin JA: Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. JAMA 2001; 286:2264–9

8. Kleinsasser A, Loeckinger A, Lindner KH, Keller C, Boehler M, Puehringer F: Reversing sevoflurane-associated Q-Tc prolongation by changing to propofol. Anaesthesia 2001; 56:248–50

9. Kleinsasser A, Kuenszberg E, Loeckinger A, Keller C, Hoermann C, Lindner KH, Puehringer F: Sevoflurane, but not propofol, significantly prolongs the Q-T interval. Anesth Analg 2000; 90:25–7

10. Kuenszberg E, Loeckinger A, Kleinsasser A, Lindner KH, Puehringer F, Hoermann C: Sevoflurane progressively prolongs the QT interval in unpremedicated female adults. Eur J Anaesthesiol 2000; 17:662–4

11. Schwartz PJ, Montemerlo M, Facchini M, Salice P, Rosti D, Poggio G, Giorgetti R: The QT interval throughout the first six months of life: A prospective study. Circulation 1982; 66(3):496–501

12. Dubin A, Kikkert M, Mirmiran M, Ariago R: Cisapride Associated with QTc Prolongation in very low birth weight preterm Infants. Pediatrics 2001; 107: 1313–6

13. Berul CI, Sweeten TL, Dubin AM, Shah MJ, Vetter VL: Use of the rate-corrected JT interval for prediction of repolarisation abnormalities in children. Am J Cardiol 1994; 74:1254–7

14. Maraban E: Cardiac channelopathies. Nature 2002; 145:213–8

15. Mitcheson JS, Chen J, Lin M, Culberson C, Sanguinetti MC: A structural basis for drug induced QT syndrome. Proc Natl Acad Sci USA 2000; 97:12329–33

16. Gallagher JD, Weindling SN, Anderson G, Fillinger MP: Effects of sevoflurane on QT interval in a patient with congenital long QT syndrome. Anesthesiology 1998; 89: 1569–73

17. Abe K, Takada K, Yoshiya I: Intraoperative torsade de pointes ventricular tachycardia and ventricular fibrillation during sevoflurane anesthesia. Anesth Analg 1998; 86:701–2