

# Sevoflurane and QTc Prolongation

## *An Interesting Observation, or a Clinically Significant Finding?*

**S**ERIOUS adverse drug reactions are frequently recognized only after postmarketing surveillance has begun. The most common cause of drug restriction or drug withdrawal from the marketplace is prolongation of the QT interval with an associated finding of polymorphic ventricular tachycardia, also known as torsades de pointes (TdP).<sup>1</sup> At least nine structurally unrelated drugs have been removed from the US market or have had their use severely limited. In this issue of ANESTHESIOLOGY, Han *et al.*<sup>2</sup> have demonstrated a dose-response relationship between sevoflurane and QTc prolongation. The observation that potent inhalation anesthetics can cause prolongation of the QT interval is not a new finding. Several studies have previously shown that other volatile anesthetics can cause QT prolongation; however, the results have not been consistent.<sup>3-5</sup> The experimental design employed by Han and colleagues is the first to employ generally accepted pharmacodynamic principles in an attempt to quantify the changes in the QTc interval that occur with the administration of sevoflurane over a clinically meaningful range of end tidal concentrations. Adult patients (N = 21) served as experimental subjects. All underwent an inhalation induction with sevoflurane with no other medications having been administered preoperatively. This “clean” study design eliminated many effects of other factors that might have influenced the QTc interval directly or indirectly. Nineteen of the subjects in this trial had increasing QTc intervals as the end-tidal sevoflurane concentration increased to a mean maximal value of  $4.3 \pm 0.33\%$ . The difference in observed mean maximal QTc prolongation compared with baseline values was  $46.1 \text{ ms}$  ( $397.8 \pm 17.5 \text{ ms}$  *vs.*  $351.7 \pm 15.4 \text{ ms}$ ), which represents a 13% increase from baseline. It is interesting to note, however, that two patients had their maximal QTc prolongation at 1% end-tidal sevoflurane, followed by a gradual decrease in QTc despite increasing sevoflurane concentrations.

The obvious question which must be asked is: “Should anesthesiologists alter their practice in light of these findings?” The process of arriving at an answer is not simple. Clinical, electrophysiological, and genetic research over the past decade or more has increased our understanding of both drug-induced and congenital long QT syndrome (LQTS),

both of which increase the likelihood of TdP. These areas of research have improved our understanding of the basic mechanisms responsible for this and other potentially lethal ventricular dysrhythmias. Guidelines have been published which attempt to predict whether a new drug may have an increased risk for TdP.<sup>6,7</sup> However, the ability to predict accurately which drug will increase the occurrence of potentially lethal dysrhythmias is inexact. This is true for both individual patients and patient populations.

HERG (Human Ether-à-go-go Related Gene) codes for a protein known as the Kv11.1 potassium ion channel which mediates the repolarizing I-Kr current in the cardiac action potential. This channel can be inhibited by both drugs and relatively rare mutations. Either can result in QT prolongation and potentially in TdP, with its increased risk of sudden death. Congenital LQTS can, however, result from the mutation of many different genes.<sup>8</sup> Although frequently characterized by an actual prolongation of the QT interval, individuals with “normal” QT intervals may carry a gene mutation that can lead to TdP and other ventricular dysrhythmias. There are hundreds of genetic mutations within the 10 genes that have been implicated in LQTS. Of these, LQT1, LQT2, and LQT3 are responsible for most of the clinical cases of LQTS. Each of these genes encodes cardiac ion channels and membrane proteins responsible for ventricular repolarization. The incidence of these mutations is estimated to be at least 1 per 2,000 persons.<sup>9,10</sup> Most of these mutation carriers remain asymptomatic,<sup>11</sup> resulting in a much lower frequency of clinical disease.

As noted above, all forms of LQTS, congenital and acquired, are characterized by abnormalities of repolarization. The QT interval represents both ventricular depolarization and repolarization, which results from the transmembrane flow of ions. The depolarizing currents are mainly the result of the inward flow of sodium and calcium ions, whereas repolarization is characterized by the outward flow of potassium ions. Abnormalities in repolarization caused by potassium channel blockers are believed to be responsible for TdP in acquired LQTS.<sup>12</sup> It is thought that a reduction in the net

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repolarizing current may be responsible for congenital LQTS.

Virtually all drugs known to cause TdP block the rapidly activating component of the delayed rectifier potassium current I-Kr. The list of drugs that may prolong the QT interval and thus contribute to ventricular dysrhythmias is far too long to review in this editorial. The interested reader is referred to the Arizona Center for Education and Research on Therapeutics (AzCERT)\* for a comprehensive listing. Frequently, these drugs are grouped into two broad categories: nonantiarrhythmic and antiarrhythmic. The most well known nonantiarrhythmic drug associated with prolonged QT and TdP, at least to anesthesiologists, is, of course, droperidol. Among the antiarrhythmic medications there are a variety of so-called pure class III antiarrhythmic agents, such as dofetilide or ibutilide, which, although effective in treating atrial fibrillation and flutter as well as ventricular tachyarrhythmias, are associated with sometimes fatal TdP, despite relatively modest increases in the QT interval. Conversely, the drug amiodarone, originally synthesized as an antianginal agent, has been associated with a negligibly low incidence of TdP, even though the drug can produce QT lengthening from 500 to 700 ms.<sup>13</sup> The reasons for this paradox are not entirely clear. Equally puzzling is the fact that not all drugs causing TdP are potent I-Kr blockers, and I-Kr block is not necessarily associated with TdP.<sup>14</sup> One must therefore assume that there must be other properties of drugs associated with TdP which predispose to this arrhythmia.

In addition to the congenital forms of LQTS and the long list of drugs associated with the development of TdP, there are numerous other risk factors, including female gender,<sup>15</sup> hypokalemia,<sup>16,17</sup> conversion from atrial fibrillation,<sup>18</sup> congestive heart failure,<sup>19</sup> digitalis therapy,<sup>20</sup> and bradycardia,<sup>16,17</sup> to name only a few. In addition, pharmacokinetic and pharmacodynamic interactions may also play a role in drug-induced QTc prolongation and increased risk for TdP.<sup>21</sup> A given patient may therefore have multiple risk factors present. The presence or absence of these risk factors may help in predicting the risk for an individual patient. For instance, female gender is a strong predictor for the risk of TdP in patients with both congenital<sup>22</sup> and acquired<sup>15</sup> LQTS.

There is a tacit assumption by the Food and Drug Administration that even a small increase in QT interval caused by a drug will also increase the risk of TdP in the population if large numbers of patients are exposed. Changes in QT interval of as little as 5–10 ms have resulted in the withdrawal from the marketplace of some noncardiovascular drugs.<sup>23,24</sup> The measured baseline QTc interval value reported by Han *et al.*<sup>2</sup> was  $351.1 \pm 15.4$  ms. This was increased to a mean maximal value of  $397.8 \pm 17.5$  ms after exposure to sevoflu-

rane. This markedly exceeds the threshold for QT prolongation noted above; however, the QTc interval even after exposure to sevoflurane was below the upper limit of normal for the QT interval (less than 430 ms for males and less than 450 ms for females†) and substantially below the high risk category of 500 ms generally accepted for congenital LQTS. Although it has been suggested that there is no linear relationship between the risk of TdP and either QT interval or the amount of QT interval prolongation resulting from drug therapy,<sup>25</sup> others have suggested that there is an increased risk of TdP associated with the magnitude of QT prolongation.<sup>26</sup> An analysis of 30 nonantiarrhythmic QT prolonging drugs showed that the average QTc prolongation in those drugs strongly associated with the development of TdP was 19.3 ms, whereas the mean prolongation in those drugs having a borderline association with TdP was 8.0 ms. Heart rate may also play an important role in the risk of developing TdP. It has been suggested that a nomogram which makes use of a QT-RR cloud diagram may be useful in determining clinically relevant risk for evaluating drug-induced QT prolongation.<sup>27</sup>

The QT prolongation reported by Han *et al.*<sup>2</sup> is much greater than the average 19.3 ms increase noted with drugs strongly associated with the development of TdP; however, it is strikingly less than the prolongation reported in other related studies. For instance, Charbit *et al.*<sup>28</sup> reported a QTc interval of  $439 \pm 29$  ms in a group of 85 patients who had received general anesthesia but had not received any prophylactic antiemetics.<sup>28</sup> Of those patients, 21% had a QTc interval that exceeds the gender-specific upper limits of normal for QTc as noted above. The specific anesthetic regimen was not specified in that report; however, it seems safe to assume that volatile anesthetics were used in a majority. The substantial difference in QTc prolongation reported by Han *et al.*<sup>2</sup> compared with Charbit *et al.*<sup>28</sup> highlights the importance of other factors that can contribute to prolongation of the QT interval in the real-world practice of anesthesia.

The time course for the development of TdP after the administration of a drug that lengthens QTc is unknown, whether one considers the population as a whole or patients with congenital LQTS. It is also unknown whether a return of the QT interval to baseline after a drug-induced QT prolongation also returns the risk of developing TdP to “normal.” It seems safe to assume that large numbers of patients anesthetized using volatile anesthetics experience prolongation of the QT interval. The duration of this prolongation is not known. However, if the risk for TdP is in fact directly and temporally related to the lengthening of the QT interval, it seems likely that TdP would be observed in the operating room with some degree of frequency. It has been estimated that 1 in 10,000 patients actually have clinical expression of the gene mutations leading to congenital LQTS. It must also be assumed that these patients are inherently at higher risk for TdP when exposed to drugs that further increase QT interval. With those assumptions in mind it is surprising that there is not a reported incidence of TdP occurring during

\* Available at: <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>. Accessed July 16, 2010.

† Available at: [http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s\\_01\\_Ruskin/sld023.htm](http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_01_Ruskin/sld023.htm). Accessed July 16, 2010.

surgery or in the immediate postoperative phase of recovery. Sevoflurane has been on the market for approximately 20 years. During that time millions of patients have received it as part of their anesthetic regimen. Postmarketing surveillance has been successful in identifying rare side effects not recognized before release,<sup>29,30</sup> although it has been recognized that there may be substantial underreporting of side effects such as TdP<sup>31</sup> because the assumption may be that observed dysrhythmias were the result of underlying disease. It is also possible that the increased risk of TdP with sevoflurane, if indeed there is one, is so low as to be undetectable. In a cohort of 291,188 surgical patients receiving either general anesthesia or neuraxial block over a 7-yr period, only three patients could be identified who experienced TdP during the 48 h after surgery.<sup>32</sup> The percentage of patients receiving sevoflurane was not specified but could reasonably be expected to be high.

Sevoflurane does appear to increase QTc in a dose-dependent manner; however, the increase in QTc which is caused by sevoflurane alone seems modest. Although the QTc prolongation reported by Han *et al.*<sup>2</sup> is statistically significant, it is not apparent that it is clinically relevant. Perhaps as important as the effect of sevoflurane alone is the effect of the entire anesthetic milieu. The cumulative effects of underlying disease, electrolyte abnormalities, adrenergic tone, temperature, circadian variation, and other drugs that are administered either acutely or chronically may result in QTc prolongation that dwarfs the effect of sevoflurane alone. The extraordinarily low incidence of TdP that occurs in the perioperative period would seem to provide some assurance that sevoflurane is in fact both an effective and a safe anesthetic. There is certainly little evidence to support the idea that other anesthetics may be inherently safer. Nevertheless, questions remain. Should our monitoring and evaluation of QTc be more rigorous throughout the entire perioperative time frame? Should our monitors make use of real-time analysis of QTc interval with appropriate alarms? If so, what is a "safe" QTc interval for patients undergoing general anesthesia? Should we avoid other drugs that are known to prolong the QT interval? And if so, which ones and under what circumstances? What is the time course over which QTc returns to baseline after general anesthesia, and does the risk of dysrhythmia decrease in a linear fashion? The answers to these questions are unknown. We do know that modern anesthesia is extremely safe. Modifying our practice based on the surrogate marker of the QTc prolongation seen with sevoflurane does not seem prudent. Huge strides have been made over the past decade in identifying the genetic abnormalities that give rise to LQTS. The electrophysiological mechanisms that lead to dysrhythmias associated with both congenital and drug-induced LQTS have been more completely clarified at the cellular and subcellular level.<sup>33</sup> A heightened awareness by clinicians of the possibility of dysrhythmias arising from QT prolongation during anesthesia should help to identify whether TdP does occur during anesthesia and under what circumstances. It is, of course, impossible to prove a negative.

We will never be able to say with absolute certainty that TdP is not associated with the QTc prolongation seen with the administration of sevoflurane or other volatile anesthetics. We can, however, take some comfort in the long track record of safety seen with the 20-yr history of the use of sevoflurane.

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