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The possible role of propofol in drug-induced torsades de pointes: A real-world single-center analysis☆

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ABSTRACT

Background: Torsades de pointes (TdP) is a polymorphic ventricular tachycardia associated with QT prolongation. Propofol is a sedative-anesthetic with proarrhythmic effects on cardiac myocytes. We performed a retrospective study to determine the incidence of TdP following propofol exposure at Mayo Clinic (Rochester, MN) from 08/11/1998–11/20/2015.

Methods: We queried our database using key search terms to identify patients exposed to propofol who developed TdP perioperatively or during non-surgical sedation. QT intervals were obtained from electrocardiograms (ECGs) performed before propofol exposure and after documented TdP and were corrected using Fridericia and Framingham methods. T wave peak-to-end (Tp-e)/QT ratios were also calculated.

Results: A total of 628,784 patients received propofol over 17.3 years. Of these patients, 21 developed TdP (12, postoperatively; 3, intraoperatively; 6, during sedation). There were 17 patients who were exposed to at least one factor associated with QT-prolongation, including QT-prolonging medications in 8 patients, heart rate <60 beats per minute in 8 patients, potassium <3.5 mmol/L in 4 patients, magnesium <1.8 mg/dL in 2 patients, and subarachnoid hemorrhage in 2 patients. The number of patients with QTc > 500 ms using Fridericia correction was significantly higher from baseline following exposure to propofol (1 patient vs 6 patients, $P = 0.04$); however no significant difference was observed with Framingham correction.

Conclusion: In our study, TdP after propofol administration occurred with an annual incidence of 1.93 per million and was often associated with other risk factors. Nevertheless, propofol should be administered with caution in patients at risk of developing TdP.

1. Introduction

Torsades de pointes (TdP) is a polymorphic ventricular tachycardia associated with prolongation of the QT interval [1]. This electrocardiogram (ECG) manifestation occurs due to prolonged repolarization of the cardiac myocyte action potential, which increases the susceptibility to early after depolarizations that trigger the arrhythmia [2]. Acquired QT prolongation may be caused by medications, hypokalemia, hypomagnesemia, bradycardia, myocardial ischemia, intracoronary contrast injections, recent resuscitation, and subarachnoid hemorrhage [3–6]. Of these factors, perioperative TdP has most commonly been preceded by hypokalemia, bradycardia, and exposure to QT-prolonging medications [7]. QTc values > 500 ms are associated with an increased risk of cardiac events [8]. In addition, a T-wave peak-to-end interval (Tp-e)/QT interval ratio (Tp-e/QT) of >0.28 has been found to be a reliable predictor of TdP in patients with acquired QT prolongation [9–10].

The sedative-anesthetic, propofol, has proarrhythmic and antiarrhythmic effects [11]. In cardiac myocytes, propofol can block sodium, potassium, and calcium channels, and decrease myocardial contractility. It can also block hyperpolarization-activated cyclic nucleotide-gated, or 'funny', channels in the sinoatrial node, causing bradycardia. The median effective concentration (EC50) of propofol used for sedation in various studies ranges from 2.05 to 4.32 μg/mL [12–14]. Propofol's effect on the QT interval is controversial. Some studies have shown minimal QT interval change with propofol, however both QT prolongation and QT shortening have been demonstrated during anesthetic induction [15–17]. TdP has also been reported after propofol administration in the absence of QT prolongation [18]. Whether TdP following propofol

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infusion is an idiosyncratic reaction or a true risk is unclear. Unfortunately, there is little definitive real-world data pertaining to propofol and the risk of TdP. In this study, we sought to determine the incidence of TdP in patients who received propofol for anesthesia. By doing so, we hoped to shed light on the safety of propofol related to drug-induced QT prolongation as it is the most widely used sedative-anesthetic agent worldwide.

2. Methods

This retrospective, observational study was approved by the Mayo Clinic Institutional Review Board. We queried the Mayo Clinic (Rochester, MN) electronic health records database for patients who received propofol from August 8, 1998, to November 20, 2015. We initially screened patients for the occurrence of TdP using ICD-9 codes; however, this yielded very few results. We then screened for cases by searching the database for clinical notes containing the key search terms *torsades* and *propofol*, which were then manually adjudicated. Documentation of TdP occurrence was sufficient to identify cases due to the low likelihood of capturing the arrhythmia on ECG. Patients were included if they were at least 18 years old and had TdP perioperatively or during nonsurgical sedation. In addition to having a baseline ECG, patients were included if a subsequent ECG had been obtained on the same day that TdP was reported. Patients were excluded if they had a history of inherited long-QT syndrome or if TdP occurred before exposure to propofol. Demographic data, concomitant QT-prolonging medications, and laboratory data (including magnesium and potassium levels) were abstracted.

Data collected from the ECGs of the study patients who developed TdP included heart rate and QT intervals. The ECGs were printed at the standard paper speed of 25 mm/s. The QT interval provided on the ECG was overread by manually measuring the QT interval in lead V5 on printed paper. Three separate cardiac cycles were measured and a mean value of the QT interval was obtained. The QTc was calculated by using the Fridericia formula (QT interval/cube root of the R-R interval) and the Framingham formula (QT interval + 0.154 × [1 − R-R interval]). These formulas were chosen for QT interval correction because they have been shown to be accurate predictors of 30-day and 1-year all-cause mortality when compared to other formulas for QT correction [19]. For increased specificity, the number of patients with prolonged QTc was determined for the standard QTc cutoff values (QTc > 440 ms for men, QTc > 460 ms for women) and the 99th percentile cutoff values (QTc > 470 ms for men, QTc > 480 ms for women) [20]. Tp-e intervals were measured in either lead V5 or V6 and Tp-e/QT ratios were calculated with values >0.28 considered prolonged. For each patient, the QTc and Tp-e/QT ratio were compared on ECGs obtained at baseline and after propofol exposure.

The Chi-Square test was used to calculate the *P* value for the difference in the number of patients with QT prolongation after exposure to propofol. A paired, two-tailed *t*-test was used to calculate the *P* value for the differences between the mean values of the QTc and the Tp-e/QT ratio at baseline and after propofol exposure. Statistical analyses were performed using JMP Statistical Discovery software (SAS, version 10).

3. Results

A total of 628,784 patients received propofol during the study period of 17.3 years. Of these patients, 21 developed TdP during or after exposure to propofol (approximately 1 in 30,000 patients). Not included in this analysis were 2 patients who were diagnosed with TdP at outside hospitals, 2 patients who developed TdP before propofol exposure, and 1 patient who developed a type I Brugada pattern on the ECG. TdP occurred intraoperatively in 3 of the 21 patients, postoperatively in 12 patients, and during nonsurgical sedation in 6 patients (Table 1). There were 17 patients in which at least one QT-prolonging factor was identified (Fig. 1). TdP was preceded by a cardiac condition in 12 patients and by subarachnoid hemorrhage in 2 patients (Table 2). Medications known to prolong the QT interval had been administered to 8 patients at the time of TdP (Table 2). These medications included amiodarone, fluoxetine, ciprofloxacin, norfloxacin, posaconazole, and tacrolimus. In addition, bradycardia occurred in 8 patients before TdP developed (2 instances were intraoperative). Electrolyte imbalances occurred in 6 patients: hypokalemia in 4 patients and hypomagnesemia in 2 patients. Although potassium levels were available for all 21 patients around the time of TdP, magnesium levels were available for only 15 patients.

Table 1
Distribution of patients with torsades de pointes.

Context	Frequency, no. (%) (N = 21)
Intraoperative	
Cardiac surgery	1 (4.8)
Noncardiac surgery	2 (9.5)
Sedated postoperatively	
Cardiac surgery	7 (33.3)
Neurosurgery (after subarachnoid hemorrhage)	1 (4.8)
Other surgery	2 (9.5)
After coronary stenting (with cardiogenic shock)	2 (9.5)
Sedated without prior surgery	
Out-of-hospital cardiac arrest (post resuscitation)	2 (9.5)
Respiratory failure	2 (9.5)
Status epilepticus	1 (4.8)
Subarachnoid hemorrhage	1 (4.8)

At standard cutoff values for prolonged QTc, more patients had QT prolongation using Fridericia correction compared to using Framingham correction, both at baseline and after propofol exposure (Table 3). At the 99th percentile cutoffs and at QTc > 500 ms, the number of patients with prolonged QT interval for each method of QT correction were comparable. The number of patients with QTc > 500 ms using Fridericia correction was significantly higher from baseline following exposure to propofol (1 patient vs 6 patients, $P = 0.04$). No significant difference was observed in the number of patients with Tp-e/QT > 0.28 at baseline and after exposure to propofol.

There was no significant difference in the mean QTc at baseline and after exposure to propofol ($P = 0.56$ for Fridericia, $P = 0.25$ for Framingham). The QTc increased after propofol exposure in 13 patients using Fridericia correction (Fig. 2) (mean, 51 ms; $P = 0.004$) and in 12 patients using Framingham correction (Fig. 3) (mean 91 ms; $P = 0.004$); After propofol exposure, the QTc decreased in 8 patients using Fridericia correction (mean 58 ms; $P = 0.04$) and in 9 patients using Framingham correction (56 ms, $P = 0.05$). The Tp-e/QT ratio increased in 14 patients (mean 0.07, $P < 0.001$) and decreased in 7 patients (mean 0.05, $P = 0.008$) after propofol exposure (Fig. 4).

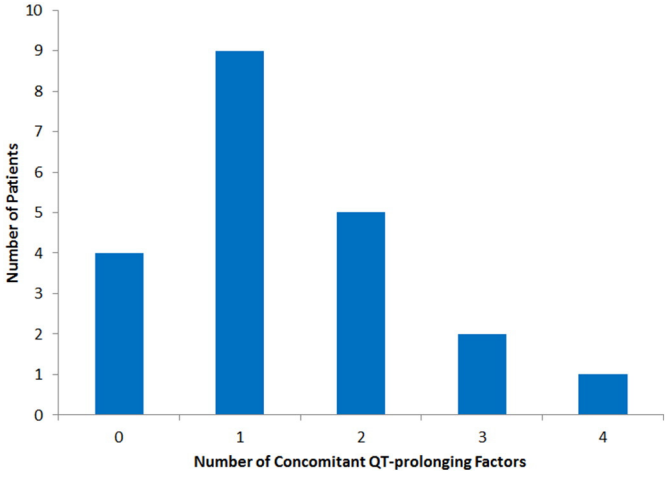

Fig. 1. Patient exposure to concomitant QT-prolonging factors.

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