Safe Single-Dose Administration of Propofol in Patients with Established Brugada Syndrome: A Retrospective Database Analysis

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Background: *Propofol is an anesthetic drug with a very attractive pharmacokinetic profile, which makes it the induction agent of choice, especially in day-case surgery. Data on its potential proarrhythmic effects in patients with Brugada syndrome (BS) patients are still lacking. The aim of our study was to investigate whether a single dose of propofol triggered any adverse events in consecutive high-risk patients with BS.*

Methods: *All consecutive patients with BS having undergone an implantable cardiac defibrillator implantation under general anesthesia were eligible for this study. The anesthetic chart of each patient was reviewed, and the occurrence of malignant arrhythmic events as well as the need for defibrillation during induction and maintenance of anesthesia was investigated. Further monitoring of the patient comprised five-lead electrocardiogram (ECG), pulse oxymetry, and continuous carbon dioxide monitoring through side sampling from the ventilator tubes. Anesthesia was induced with propofol and sufentanyl. Injection of propofol occurred in a single-shot bolus—as often performed by most anesthetists—over a few seconds. Anesthesia was maintained with volatile anesthetics (sevoflurane or desflurane) in an oxygen-air mixture.*

Results: *From 1996 to 2011, 57 high-risk patients with BS (35 males; mean age: 43 ± 16 years) underwent an automated implantable cardioverter defibrillator implantation at our center using propofol as induction drug of general anesthesia. Three patients had a history of spontaneous type I ECG, three had aborted sudden death, and 51 had a history of recurrent or unexplained syncope. The induction dose ranged between 0.8 mg/kg and 5.0 mg/kg (2.2 ± 0.7 mg/kg). Only one case received propofol to maintain anesthesia. The surgical procedure involved an anesthetic period of 75 ± 25 minutes. No patient developed a malignant rhythm during induction and maintenance of anesthesia. All patients were then safely discharged from the postanesthetic care unit after 1 hour. No adverse events were noticed during the recovery phase. In our study, administration of a single-dose propofol in patients with BS was safe. Nevertheless, extreme caution is still recommended when conducting general anesthesia in patients with BS, especially if BS patients are sedated with propofol for longer periods. (PACE 2013; 00:1–6)*

propofol, general anesthesia, Brugada syndrome

Introduction

Brugada syndrome (BS) was first described in 1992 and is characterized by the presence of coved-type ST-segment elevation in the right precordial leads (V1–3) and increased risk of sudden death (SD).[1] BS is considered to be a primary electrical disease (channelopathy) due to mutations in the myocardial sodium channel gene *SCN5A* and other genes, associated with an increased propensity to develop malignant ventricular arrhythmias (VAs).[2] It is inherited in an autosomal dominant manner with incomplete penetrance.[3] Furthermore, although macroscopic heart examination in patients with BS is normal,

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some authors have reported some subtle structural abnormalities in the right ventricular outflow tract.[4–9]

Since the introduction of systematic and active screening of patients with aborted SD or syncope with class I antiarrhythmic drugs (AADs), the diagnosis and incidence of BS has increased considerably. This implies that anesthetists and critical care physicians, who administer intravenous anesthetics, are likely to be more often confronted with patients diagnosed with this syndrome.

Propofol is one of the most frequently used intravenous anesthetics. The effects of propofol on cardiac sodium channels and ionic currents have been investigated in studies *in vitro*.[10] Although the proarrhythmic and antiarrhythmic abilities of propofol have been already reported, there is still conflicting opinion concerning its use in patients with BS and data on its potential proarrhythmic effects in large populations of BS patients are still lacking.[11–20]

Propofol has a very attractive pharmacokinetic profile, which makes it the induction agent of choice, especially in day-case surgery.[21,22] To the best of our knowledge, up to date, no study has investigated the administration of a single dose of propofol in high-risk patients with BS requiring an automated implantable cardioverter defibrillator (AICD) implantation.

The aim of our study was to investigate whether a single dose of propofol triggered any adverse events in larger consecutive high-risk populations with BS.

Methods

Patient Population

Since 1996, all patients diagnosed with BS and their relatives tested for the syndrome have been included in a registry and followed-up in a prospective fashion. BS was diagnosed clinically according to the modified task force criteria.[23] Patients with a coved type I electrocardiogram (ECG) with $\geq$2 mm ST elevation in one or more right precordial or inferolateral leads, either spontaneously or after class I AAD administration, were diagnosed with BS.[6,23] Risk assessment was based on clinical presentation, rest ECG abnormalities, and electrophysiological study (EPS). BS patients were considered to have high-risk features if they had a history of aborted SD or syncope, in case of documented spontaneous type I ECG, and if sustained spontaneous VA was documented or induced during EPS. Until 2010, family history of sudden cardiac death at a young age was also considered a sign of high future risk of VA events.[24,25] Patients with one or more risk factors were eligible for AICD implantation for the primary or secondary prevention of SD.

All consecutive patients with BS having undergone, from 1996 to 2011, a single- or dual-chamber AICD implantation were retrospectively screened for inclusion. The implantation was performed under general anesthesia. We reviewed the anesthetic chart of each patient investigating the occurrence of malignant arrhythmic events and the need for defibrillation during induction and maintenance of anesthesia. The choice of hypnotic agent and the dose administered for induction of anesthesia were registered. General anesthesia was conducted in an operating theater where an external cardioverter defibrillator was attached to the patient with adhesive pads prior to the procedure. The radial artery was cannulated for invasive blood pressure monitoring. Further monitoring of the patient comprised five-lead ECG, pulse oxymetry, and continuous carbon dioxide monitoring through side sampling from the ventilator tubes. Anesthesia was induced with propofol and sufentanyl. The airway was secured with a laryngeal mask or an endotracheal tube. In the latter, a muscle relaxant was administered in addition. Injection of propofol occurred in a single shot bolus—as often performed by most anesthetists—over a few seconds. Anesthesia was maintained with volatile anesthetics (sevoflurane or desflurane) in an oxygen-air mixture. Nitrous oxide was not used in this study. AICD implantation was performed by a cardiac surgeon via a nonthoracotomy transvenous lead system. Upon successful implantation of the AICD, defibrillation threshold testing was conducted and the wound was sutured. No local anesthetics were further administered.

Statistics

In this study, descriptive statistics were used and values are reported in mean $\pm$ standard deviation. In case of proportions, the absolute numbers were reported followed by percentages.

Results

Extended retrospective analysis of 429 patients with BS from the aforementioned database was performed. One hundred and fifty-five patients were considered eligible for treatment with an AICD. The implantation was performed under general anesthesia in 72 cases in our hospital. The remaining 83 were treated in other hospitals. Only patients implanted with an AICD in our center were further analyzed. Induction of anesthesia was obtained with propofol in 57 patients (79%).

Table I.

Population Characteristics

Age at implantation of AICD (years)	43 ± 16
Male, n (%)	35 (61)
Spontaneous type I ECG, n (%)	3 (5)
ASD, n (%)	3 (5)
Syncope, n (%)	51 (89)
Class I AAD challenge, n (%)	57 (100)
EPS, n (%)	55 (96)
VF/VT inducibility, n (%)	21 (38)
Surgical procedure time (minutes)	75 ± 25
TTE exam, n (%)	51 (89)
TTE with normal function, n (%)	50 (100)
Single-lead AICD, n (%)	40 (70)
Dual-lead AICD, n (%)	17 (30)
Propofol for AICD (mg/kg)	2.2 ± 0.7
Surgical history for general anesthesia, n (%)	38 (67)

Demographic data of the patients with Brugada syndrome eligible for AICD implantation (total number = 57). Values are reported in mean ± Standard deviation or n (%). AAD = antiarrhythmic drugs; AICD = automated implantable cardioverter defibrillator; ASD = aborted sudden death; ECG = electrocardiogram; EPS electrophysiology study, TTE = transthoracic echocardiography; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table II.

Surgical Procedures

Patient	Gender	Weight (kg)	Propofol (mg/kg)	Surgical Procedure
7	F	56	1.8	AICD revision
9	F	75	2.1	Total hip prosthesis
15	F	68	2.4	Pseudo-aneurysm femoral artery
23	F	68	2.9	AICD repositioning
25	M	104	2.4	Flutter ablation
26	F	40	3.7	AICD revision
27	F	57	3.2	AICD revision
38	M	72	1.9	AICD lead repositioning
39	F	55	1.8	AICD repositioning
55	M	74	1.4	Lumbar disc hernia repair
57	M	94	2.1	Varicectomy

Summary of surgical procedures other than implantation of AICD in 11 patients with BS. The dose of administered propofol was 2.3 ± 0.7 mg/kg.

The mean age at implantation of the AICD and subsequently administration of propofol was 43 ± 16 years (ranging from 6 years to 76 years). Thirty-five patients (61%) were male. Three patients had a history of spontaneous type I ECG (5%), three (5%) had aborted SD, and 51 (90%) had a history of recurrent or unexplained syncope. The demographic and clinical characteristics are summarized in Table I. The induction dose ranged between 0.8 mg/kg and 5.0 mg/kg (2.2 ± 0.7 mg/kg). Only one patient received propofol to maintain anesthesia. The surgical procedure involved an anesthetic period of 75 ± 25 minutes. No patient developed a malignant rhythm during induction and maintenance of anesthesia. All patients were then safely discharged from the postanesthetic care unit after 1 hour. No adverse events were noticed during the recovery phase. Subsequent to 24 hours of monitoring, patients left the hospital in good condition.

Interestingly, 44 patients (61%) had a history of at least one surgery—that could only be performed under general anesthesia—prior to or following their AICD implantation (Table I). We retrieved anesthetic charts from 11 (25%) patients to whom propofol was administered as the induction agent (Table II). The other surgical procedures were performed elsewhere. The dose administered for induction of anesthesia was 2.3 ± 0.7 mg/kg. These procedures were also uneventful.

Discussion

Patients with BS are more prone to develop malignant arrhythmias during episodes of fever or increased vagal tone and after administration of certain medications.[6] Propofol has been proposed as a contributor to such arrhythmias. Pires et al. showed that administration of propofol on pigs behaves like a sodium channel blocker causing dose-related bradyarrhythmias, but concluded that no effect on the atrioventricular node function and on the conduction properties of atrial and ventricular tissues was found.[17] However, the existing data about the safety of propofol in patients with BS are conflicting.

The arrhythmogenic risk associated with prolonged propofol infusion was first described in 1992 by Parke et al. Five fatalities were reported upon propofol infusion.[26] A few years later, propofol infusion syndrome was described as an entity.[27] It is known that administration of high dose of propofol for prolonged periods is associated with metabolic lactic acidosis, rhabdomyolysis, bradycardia, and coved-type ST-segment elevation. Although the causative association with prolonged propofol infusion in high doses is still debatable, it is believed that it occurs probably when administered in the presence of other risk factors and comorbidities such as sepsis, traumatic brain injury, critical illness, impaired microcirculation, impaired carbohydrate supply, or increased endogenic or exogenic catecholamine levels.

Vernooy et al. already assessed the relationship between a Brugada-like ECG pattern and propofol infusion rate in a cohort of 67 head-injured patients. Seven of these cases were identified with propofol-related infusion syndrome. In six patients, a coved-type ST was identified in the right precordial lead V1 to V3; they developed VA, irrecoverable ventricular fibrillation, and deceased. They concluded that SD in patients with propofol-related infusion syndrome was associated with ST-elevation in leads V1 to V3, such as in patients with BS. This is the first indicator of electrical instability and induces a high risk for imminent death.[19]

Junttila et al. collected data on 47 patients who developed a typical Brugada-type ECG during an acute medical event.[16] During this event, fever was a common finding in 16 patients. Electrolyte imbalances were the culprit in five patients. Due to drugs or medication, ECG abnormalities were found in 26 patients. In seven patients, ECG abnormalities were associated with propofol. They reported that propofol was responsible for inducing SD in five patients and VT in one patient. One patient did not develop further symptoms. In contrast to our population, these patients had ECG abnormalities during the presence of an acute event. Clinical characteristics of these patients and the type of acute event requiring sedation in the aforementioned seven patients were not reported. The administered dose of propofol and the infusion period were not reported either; therefore, we cannot compare our findings. In this study, we analyzed patients who had BS with high risk for VA and received propofol under controlled circumstances for an elective surgical procedure. Thus, abnormal clinical conditions as fever, electrolyte imbalances, and electrocardiographic abnormalities were excluded in all patients before elective surgery. If conditions were not optimal, surgery was postponed. When a patient suffers from an acute event, possibly with underlying comorbidity and administration of multiple drugs, it is often difficult to prove a causative association with one drug. Propofol is a commonly used anesthetic in acute circumstances when sedation is required because of its favorable pharmacokinetic profile.

Electrocardiographic changes during administration of propofol have been reported in the literature. Richter and Brugada reported a case of a young man who developed a Brugada-like coved-type ECG during catheter ablation of paroxysmal atrial fibrillation under propofol sedation. After discontinuation of propofol, he perceived a normalization of the ECG.[28] In contrast to our studied population, this patient was deeply sedated for a prolonged period (less than 2 hours) with continuous propofol infusion presumably under spontaneous breathing. It is unclear whether the respiratory conditions were monitored. In our study, an anesthetist secured the airway of each patient after induction of anesthesia, monitoring and controlling mechanical ventilation throughout the surgical procedure. Continuous end-tidal carbon dioxide during anesthesia provided important information concerning the airway and ventilation, and subsequently a good reflection of the arterial carbon dioxide tension of each patient. Hypercapnia due to inadequate ventilation or rebreathing is known to trigger severe arrhythmic events. It is possible that discontinuation of the sedation—in the reported case—which resulted in awakening of the patient and restoration of adequate breathing would lead to normalization of the ECG. Another crucial difference is that the reported patient was asymptomatic and had a negative class I AAD.

Clinical characteristics and data on propofol administration during and after general anesthesia of 57 BS patients with high-risk features were retrospectively analyzed in this study. The mean duration between diagnosis of BS and AICD implantation was 218 $\pm$ 533 days. Therefore, we believe that general anesthesia was conducted at a moment when BS patients were most prone to develop new malignant events. The main finding of this study is, however, that no arrhythmic events were induced followed by a single dose of propofol administration. This finding is consistent with other publications in the literature. Several authors have reported cases where the general anesthesia with propofol in patients with BS was uneventful.[18,29–36]

As no arrhythmic event had been induced after a single dose of propofol, other previously described risk factors associated with increased risk for arrhythmic events, such as spontaneous type I ECG and previous history of syncope or aborted sudden death, could not be analyzed as possible outcome predictors.[6,25]

Despite the fact that propofol has attracted conflicting interest concerning patients with BS, it was administered in the majority of the reported anesthetic procedures. To the best of our knowledge, there is no irrefutable evidence to avoid the use of propofol in patients with this channelopathy, especially in a single bolus. In this study, we observed that more than half of our analyzed patients had safely undergone other surgical procedures also. We obtained and confirmed these data for 11 (25%) patients who underwent their surgical procedure after conduction of anesthesia with propofol. This would also support the argument for safe induction of

anesthesia with single dose of propofol in the elective surgical patient with BS.

To date, it remains unclear whether the apparently similar ECG pattern observed in patients developing propofol infusion syndrome and patients with BS developing a malignant arrhythmia is based on a common mechanism or is an expression of a phenotypic similarity. This does not necessarily suggest that patients with BS are forbidden to have propofol as an induction agent. Nevertheless, caution should be advised until prospective studies are able to confirm our findings.

Limitations of the Study

This study is based on a retrospective data analysis. However, we believe that the size and characteristics of our study population produced a homogenous cohort group—of patients suffering from an uncommon disorder—revealing results of great clinical importance. Electrocardiographic changes may have been missed, especially if they occurred with minimal or no hemodynamic deterioration. Standard electrocardiographic monitoring of the surgical patient does not require a 12-lead ECG, but remains the best way to identify a type I or type II ECG.

Conclusion

In our study, administration of a single-dose propofol in patients with BS undergoing AICD implantation proved to be safe. Nevertheless, extreme caution is still recommended when conducting general anesthesia in patients with BS, especially if BS patients are sedated with propofol for longer periods. It is of utmost importance that anesthetists and critical care physicians recognize a BS ECG and are aware of the possible clinical presentation and hemodynamic repercussions during administration of AAD. Prospective studies should be conducted in order to diminish speculations and uncertainty so that the administration of propofol in patients with BS may no longer be a matter of belief or false conviction.

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