

# Drug-Related Cardiac Arrest During Open Craniotomy

Dilek Erdogan Ari\*

Department of Anesthesiology and Reanimation, Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey

\*Corresponding author: Dilek Erdogan Ari, Department of Anesthesiology and Reanimation, Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey, E-mail: [dilekerdoganari@gmail.com](mailto:dilekerdoganari@gmail.com)

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## Abstract

Although fatal cardiac arrest is a known complication of intravenous phenytoin, most practitioners are not aware of the toxicity of phenytoin on the conduction system. We present a patient who developed asystolic cardiac arrest during intravenous administration of phenytoin in open craniotomy.

## Introduction

Phenytoin is used for the management of generalized tonic-clonic seizures, simple or complex partial seizures and status epilepticus, as well as for the treatment and prevention of seizures during or following head trauma or neurosurgery [1]. Besides, phenytoin is a class IB antiarrhythmic agent and has different effects on cardiac tissue [2]. Intravenous phenytoin can cause dysrhythmias, hypotension and cardiovascular collapses [3]. Although fatal cardiac arrest is a known complication of intravenous phenytoin [4], most practitioners are not aware of the toxicity of phenytoin on the conduction system [5]. Oral phenytoin toxicity causing sinus arrest has also been reported [5]. In order to rise the awareness about cardiac risks of phenytoin among the clinicians, we present a recently encountered patient who developed asystolic cardiac arrest during intravenous administration of phenytoin in open craniotomy.

## Case Report

A 100 kg, 54 years old man was scheduled for open craniotomy for resection of a hypophysal benign tumor in an educational and research hospital in Turkey. The medical history revealed no systemic disease except hypertension medicated with valsartan-hydrochlorothiazid combination. Prior to surgery, serum chemistries were within normal limits. The baseline electrocardiogram revealed sinus rhythm with, a first degree atrioventricular block, a QT of 433 ms and a corrected QT of 466 ms at a rate of 69 beats/min. Following monitorization with ECG, left radial artery blood pressure and SpO<sub>2</sub>, basal heart rate and blood pressure were respectively 70 b/min and 170/70 mm Hg before anesthesia induction. Anesthesia was induced by 200 mg propofol, 200 mcg fentanyl, 2 mg midazolam and 50 mg rocuronium and maintained with total intravenous anesthesia using propofol (6 mg/kg/h) and remifentanyl (0.06 mcg/kg/min). The patient received an infusion of phenytoin at a rate of 10 mg/min in order to prevent seizures related to surgical manipulation. Twenty minutes after the beginning of phenytoin infusion, he suddenly developed a deep bradycardia resulting in asystole. The administration of phenytoin and remifentanyl was stopped. Treatment with atropine was implemented immediately. The patient's heart rate and blood pressure recovered shortly thereafter. Remifentanyl infusion was restarted and the surgeon was allowed to continue to the operation. The rest of the operation was achieved uneventfully. The patient was extubated and discharged to neurosurgery clinic with stable haemodynamics.

## Discussion

Despite its low incidence, intraoperative cardiac arrest is a potentially catastrophic event, leading to a high mortality rate [6]. Complicating patient, anesthetic, and surgical factors can be associated with the incidence and survival outcomes of cardiac arrest in the operating room [6]. Although cardiac arrest due solely to anesthesia and mainly related to medication and airway issues can still occur in clinical practice, its incidence has been gradually decreasing in modern anesthetic practice, and patients with anesthesia-related cardiac arrest show a higher survival rate than those with intraoperative cardiac arrest due to other causes. In the study conducted by Kim et al. [6], the overall incidence of intraoperative cardiac arrest due to all causes was reported as 2.67 per 10000 anesthetic cases. The main cause of cardiac arrest was hypovolemia, followed by cardiac origin [6]. Ellis et al [7] identified 160 perioperative cardiac arrests within 24 h of surgery from an anesthesia database of 217,365 cases. Fourteen cardiac arrests were anesthesia-attributable, resulting in an incidence of 0.6 per 10,000 cases. Twenty-three cardiac arrests were found to be anesthesia-contributory resulting in an incidence of 1.1 per 10,000 cases. Anesthesia-related cardiac arrest occurred in 37 of 160 cardiac arrests within the 24-h perioperative period. Sixty-four percent of anesthesia-attributable cardiac arrests were caused by airway complications that occurred primarily with induction, emergence, or in the postanesthesia care unit.

Hypotension and bradycardia usually occur when the infusion rate of phenytoin exceeds 50 mg/min, although episodes have been reported at slower infusion rates [2]. Rates for elderly patients and those with cardiovascular disease should be lower than 25 mg/min [1]. Randazzo et al. [2] reported a case of complete atrioventricular block with ventricular asystole in a patient receiving intravenous phenytoin. The patient underwent left craniotomy and resection of a tumor mass in the left frontal lobe. The baseline surface electrocardiogram (ECG) revealed sinus rhythm with left anterior fascicular block. Eight hours postoperatively, upon receiving 50 mg phenytoin at an infusion rate of 10 mg/min, the patient developed complete AV block with ventricular asystole. Excluding all other causes for AV block and observing the temporal relation of AV block to the infusion of intravenous phenytoin, it was concluded that intravenous phenytoin caused this event [2].

Neurosurgical procedures can result in high central nervous system pressure, which can cause an elevated systemic blood pressure, as well

as an increase in vagal tone [2]. Our patient did not have elevated blood pressure; in contrast, hypotension accompanied bradycardia which rapidly converted to asystolic cardiac arrest. Additionally, he received 250 mg methyl prednisolone and 20 mg furosemide at the anesthesia induction to decrease cerebral edema, and the surgeon did not notice cerebral swelling. Thus, the cardiac arrest was not related to elevated intracranial pressure. There was no evidence of pressure on carotid bodies, which could induce AV block. The patient was not receiving any medications such as beta-blockers, calcium channel blockers, or clonidine which could cause severe bradycardia resulting in cardiac arrest. Blood gas analysis revealed no electrolyte or acid-base disturbances during the surgery.

The baseline electrocardiogram of our patient revealed mild prolongation of QTc. Propofol which was used in the anesthesia induction, has been shown to prolong QTc interval [8]. Although adverse effects are rare, bradycardia has been reported and this can lead to cardiac arrest in some patients [9]. The risk of bradycardia-related death during propofol anaesthesia was estimated to be 1.4 in 100,000 [10]. Fentanyl probably shortens the QTc in congenital long QT syndrome as well as in healthy patients [8]. Remifentanyl which induces a dose-dependent decrease in heart rate and arterial blood pressure was shown to reduce the prolongation of QTc following intubation and laryngeal mask airway insertion [8]. The lengthening of QT interval results in fatal ventricular arrhythmias like torsade de pointes. The potential therapy of long QT interval include the use of phenytoin and other sodium channel blockers [11]. Phenytoin's narrow therapeutic window, multiple drug interactions and side effect profile make it an infrequently used antiarrhythmic. It is, however, a potent antiarrhythmic agent, which may be useful in treatment of ventricular tachycardia due to QT prolongation, especially in patients with multiple drug intolerances [12]. Our patient also had a first degree A-V block preoperatively. He received simultaneous infusion of propofol, remifentanyl and phenytoin. Furosemide given at the anesthesia induction provided an urinary output 1000 ml before the occurrence of cardiac arrest. The administration of propofol, remifentanyl and phenytoin in the presence of hypovolemia due to diuresis is judged to be responsible for the development of cardiac arrest.

Supratherapeutic plasma phenytoin levels may cause Brugada pattern on ECG (right bundle branch block with ST segment elevation in leads V1-V3) which may be associated with sudden cardiac death [13]. Phenytoin's propylene glycol carrier shoulders the blame for most of these cardiac adverse effects [3]. Fosphenytoin, a more soluble phenytoin prodrug was suggested to be safely infused at triple rate of phenytoin but it has been reported to cause haemodynamically unstable bradydysrhythmias [3].

## Conclusion

In patients with preexisting disturbance of A-V conduction, and in the presence of hypovolemia, the combinations of drugs which may cause fatal

bradycardia may result in cardiovascular compromise. Clinicians should be alert about cardiac risks of phenytoin and the drug should be used with precaution in the presence of ECG and blood pressure monitorization.

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