Abstract: We present the occurrence of ‘torsade de pointes’ induced by the combination of peroperative fluconazole administration and sevoflurane anesthesia in a patient with ‘long QT syndrome’ (LQTS) scheduled for resection of a sacral abscess. Eight minutes following uneventful induction of anesthesia ‘torsade de pointes’ occurred, terminated by a counter shock. At this time the end-tidal concentration of sevoflurane was 2%. The fluconazole infusion was disconnected and the operation was continued. Post-operatively the patient awakened uneventfully. The direct postoperative ECG showed a QTc of 531 ms (preoperative QTc of 442 ms.) and remained prolonged afterwards. A long QT syndrome was the most likely diagnosis. LQTS is classified as either congenital or acquired. Patients with acquired LQTS may have an underlying predisposition for QT prolongation. Many drugs have shown to be associated with a prolonged QT interval (1). The syndrome in this particular patient was unmasked by sevoflurane. Concomitant administration of fluconazole might have further predisposed the patient to the development of ‘torsade des pointes’. Although LQTS is relatively rare, it is important for the anesthesiologist to be familiar with the disease because of the associated morbidity and mortality and the potential for anesthesia to induce malignant arrhythmias in asymptomatic carriers.

Key words: Anesthesia ; long QT syndrome ; sevo- flurane ; torsade de pointes.

INTRODUCTION

In patients with a ‘long QT syndrome’ (LQTS), malfunctioning ion channels impair ventricular repolarisation. It is an electrophysiologic disorder which predisposes to malignant ventricular arrhythmias, especially ‘torsade de pointes’. Sevoflurane anesthesia induced ‘torsade de pointes’ has been linked to three cases (1-3). We present a patient with LQTS who developed ‘torsade de pointes’ after the combination of fluconazole and sevoflurane.

CASE REPORT

A 69 year old woman (ASA III, weight 84 kg), with a history of hypertension had been surgically treated for a tuba-ovarian abscess. Postoperatively, she developed dyspnea after a new onset of atrial fibrillation with a slow ventricular response, a right bundle branch block QRS morphology and a QTc of 442 ms. A trans-thoracic echocardiogram revealed an ejection fraction of 61% with severe mitral and tricuspid regurgitation. She developed a pre-sacral abscess and the patient was scheduled for reoperation.

Two days before surgery, intravenous fluconazole treatment was started and continued during the operation. The day of the operation, the patient had received oral 1000 mg acetaminophen, 5 mg amlodipine, 4500 mg piperacillin/tazobactam, and 40 mg esomeprazole. The serum potassium concentration was 3.2 mmol/L and the patient was still in atrial fibrillation (Fig. 1A). Anesthesia was induced with 130 mg propofol and 10 mg sufentanil, and a laryngeal mask was inserted without any problem. Anesthesia was maintained with 1.5-2% end-expired sevoflurane in oxygen/air. Eight minutes after induction (Fig. 1B) ‘torsade de pointes’ developed (Fig. 1C). The patient was defibrillated (Fig. 1D) and atrial fibrillation with a slow ventricular response reoccurred (Fig. 1E). Immediately after the diagnosis of torsade, fluconazole was taught of as the causative factor and the infusion was disconnected (a maximum of 100 mg was
infused). Sevoflurane was continued as it was not suspected to cause QT prolongation at that moment. The operation was continued and the patient awakened uneventfully from general anesthesia.

The postoperative ECG showed a QTc of 531 ms, indicated by the computer. The QTc interval measured and averaged manually 5 intervals by the cardiologist was 626 ms. Blood chemistry was normal. Fluconazole was switched to caspofungin, but the QTc remained prolonged. Ischemia is an important cause of a prolonged QT interval, but without signs of ischemia during or immediately after anesthesia, and no hypotension and anemia was present to provoke ischemia. Later on, cardiac catheterization showed normal coronary arteries. The family history revealed that a brother died suddenly while cycling at age 56 and that father died during induction of anesthesia at age 68. Because a long QT syndrome was the most likely diagnosis, the patient received an implantable cardiac defibrillator (ICD) before discharge from the hospital.

**Discussion**

We describe a patient in whom a long QT syndrome was unmasked during general anesthesia with sevoflurane and fluconazole.

LQTS is classified as either congenital or acquired. Congenital LQTS is an inherited channelopathy with an estimated prevalence of about 1:5000 but with variable penetrance (4). Patients with acquired LQTS include a number of ‘silent’ carriers of congenital LQTS, and patients with functional polymorphisms of the same genes (5). Patients who eventually develop drug-induced ‘torsade de pointes’ tend to have a longer baseline QT interval. They are also at higher risk of recurrent arrhythmias if exposed to certain drugs (6).

In the adult population, normal QTc values for males are 350 to 450 ms and for females 360 to 460 ms (6). However, there is considerable overlap of the QTc interval between normal population and LQTS patients as well as considerable day-to-day variability of the QTc interval (7-9). Measuring the QTc interval may be difficult and particularly in a patient with atrial fibrillation with varying cycle lengths. Both QTc interval, measured by computer and measured manually by cardiologist, are prolonged. Our patient did have a QTc within the normal range on admission and the syndrome was only unmasked by the combined QT prolonging effect of a volatile anesthetic (sevoflurane) and the antifungal fluconazole. The persistence of the prolonged QTc interval despite the absence of other predisposing factors further pointed to a congenital form in this patient.

The hallmark arrhythmia of LQTS is ‘torsade de pointes’ (“twisting of the points”), a polymorphic ventricular tachycardia characterized by twisting of the QRS axis around the baseline. The underlying electrophysiological derangement in long QT syndrome is a marked delay in repolarisation, which predisposes to early after-depolarisations that initiate the tachycardia. It typically begins with a characteristic long-short initiating sequence also seen in our patient (Fig. 1B). Risk factors for the development of torsade de pointes are foremost the length of the QT interval and include further female gender, reduced serum potassium concentrations, adrenergic stimulation (promoted by anxiety and surgery), pronounced stimulation, and many drugs.

Drugs may influence the ion channels and further prolong or unmask the repolarisation abnormality. Many drugs (5, 10) have been associated with a prolonged QT interval. An extensive list of drugs with risk of ‘torsade de pointes’ can be found on www.torsades.org (10). Among the drugs used in anesthesia, prolongation of the QT interval by volatile anesthetics such as isoflurane (11-12) and sevoflurane (1-3, 5, 13-14) has been described. Halothane has a dose-dependent response: prolongation of the QT interval with 1% halothane and shortening of the QT interval with 2% (12). Several other drugs used in anesthesia, including ketamine, succinylcholine, pancuronium, droperidol and neostigmine may also prolong the QT interval (5). The vast majority of drugs associated with drug-induced ‘torsade de pointes’ inhibit the KCN_H2-encoded -subunit of the delayed rectifying potassium (I_K) current which is a major contributor to phase 3 repolarization in ventricular myocytes (13). Propofol tends to shorten the QTc interval and can actually rapidly reverse sevoflurane-associated QT prolongation (14-15). (Propofol is the exception, so I would mention that last.) Concomitantly administered QT prolonging drugs may increase the risk, as with fluconazole and sevoflurane in our patient.

In the acute phase, removal of any provocative drug is essential. We did not suspect sevoflurane at the time of surgery, nor did we know that propofol could shorten the QT time. Arrhythmias can also be suppressed by acceleration of the basic heart rate: there is an inverse relation between heart rate and the repolarisation time (7). Suppression of early after-depolarisations with I.V. magnesium sulphate and sedation can attenuate adrenergic mediated
triggers for ‘torsade des pointes’ (7). Anti-arrhythmic drugs such as amiodarone and sotalol may worsen the tachycardia as they prolong repolarisation.

A pre-operative history about a potential QT prolonging predisposition before induction of anesthesia is essential, especially when already a potential QT prolonging drug is administered (fluconazole). This would have revealed several risk factors for drug-induced “torsade de pointes”: female sex, hypokalemia, family history of sudden death. Also an ECG after the start of fluconazole treatment was lacking, which could have pointed to a prolonged QT interval. And finally, knowledge of the QT prolonging potential of sevoflurane in this setting would have changed the anesthesia protocol.

Fig. 1. — Recorded cardiac rhythms: cardiac rhythm (green), plethysmogram (yellow) and capnography (blue) in a patient developing ‘torsade des pointes’ during surgery under general anaesthesia with sevoflurane. Cardiac rhythm before induction of anaesthesia (A). Cardiac rhythm after induction of anaesthesia, changing from atrial fibrillation to ‘torsade de pointes’ 8 minutes after induction (B). ‘torsade de pointes’ (C). Restoration of the rhythm after 70J counter shock (D). Atrial fibrillation with a slow ventricular response (E).
CONCLUSION

We present a patient with ‘torsade de pointes’ exaggerated by sevoflurane anesthesia in the presence of several risk factors. Although ‘Long QT Syndrome’ is relatively rare, it is important to recognize the potential for anesthesia to induce malignant arrhythmias in asymptomatic carriers and to be familiar with the treatment.

References