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REVIEW ARTICLE

Drug-induced life-threatening arrhythmias and sudden cardiac death: A clinical perspective of long QT, short QT and Brugada syndromes

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KEYWORDS
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Pharmaceutical preparations

Abstract Sudden cardiac death is a major public health challenge, which can be caused by genetic or acquired structural or electrophysiological abnormalities. These abnormalities include hereditary channelopathies: long QT, short QT and Brugada syndromes. These syndromes are a notable concern, particularly in young people, due to their high propensity for severe ventricular arrhythmias and sudden cardiac death.

Current evidence suggests the involvement of an increasing number of drugs in acquired forms of long QT and Brugada syndromes. However, drug-induced short QT syndrome is still a rarely reported condition. Therefore, there has been speculation on its clinical significance, since few fatal arrhythmias and sudden cardiac death cases have been described so far.

Drug-induced proarrhythmia is a growing challenge for physicians, regulatory agencies and the pharmaceutical industry. Physicians should weigh the risks of potentially fatal outcomes against the therapeutic benefits, when making decisions about drug prescriptions. Growing concerns about its safety and the need for more accurate predictive models for drug-induced fatal outcomes justify further research in these fields.

The aim of this article is to comprehensively and critically review the recently published evidence with regard to drug-induced life-threatening arrhythmias and sudden cardiac death. This article will take into account the provision of data to physicians that are useful in the identification of the culprit drugs, and thus, contribute to the prompt recognition and management of these serious clinical conditions.

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PALAVRAS-CHAVE
Morte súbita cardíaca;
Síndrome do QT longo;
Torsades de pointes;
Síndrome do QT curto;
Síndrome de Brugada;
Preparações farmacêuticas

Arritmias potencialmente fatais e morte súbita cardíaca induzidas por fármacos: uma perspetiva clínica das síndromes do QT longo, QT curto e Brugada

Resumo A morte súbita cardíaca é um desafio significativo para a saúde pública, pode desencadear-se de anormalidades estruturais ou eletrofisiológicas, tanto genéticas como adquiridas, e abranger as assim chamadas canalopatias hereditárias: síndromes do QT longo, QT curto e Brugada. Essas síndromes são um problema considerável, particularmente para os jovens, pela sua elevada propensão para arritmias ventriculares graves e morte súbita cardíaca.

A evidência atual sugere o envolvimento de um número crescente de fármacos nas formas adquiridas das síndromes do QT longo e Brugada. No entanto, a síndrome do QT curto induzida por fármacos é ainda uma condição raramente reportada. Consequentemente, especulação tem surgido sobre o seu significado clínico, uma vez que poucos casos de arritmias fatais e de morte súbita cardíaca foram descritos até ao momento.

A pró-arritmia induzida por fármacos é um desafio crescente tanto para médicos como para entidades reguladoras e indústria farmacêutica. Os médicos devem pesar o risco de desfechos potencialmente fatais com os benefícios terapêuticos, aquando da tomada de decisões na prescrição de fármacos. As preocupações crescentes sobre a sua segurança e a necessidade de modelos preditivos mais precisos para desfechos fatais induzidos por fármacos justificam pesquisas adicionais nesses domínios.

O objetivo deste artigo foi rever, de forma abrangente e crítica, a evidência publicada recentemente, no que diz respeito às arritmias potencialmente fatais e morte súbita cardíaca induzidas por fármacos, tendo em consideração o fornecimento de dados úteis para médicos na identificação dos fármacos responsáveis e, assim, contribuir para o pronto reconhecimento e gestão desses quadros clínicos graves.

Introduction

Sudden cardiac death

Remarkably, sudden cardiac death (SCD) accounts for about a quarter of the 17 million deaths attributable to cardiovascular diseases every year worldwide.[1]

Coronary artery disease (CAD) is still the leading cause of these deaths, particularly in the elderly. However, primary cardiac arrhythmias and cardiomyopathies are the most common causes of SCD in young people.[2,3] Ventricular fibrillation (VF) is the most common arrhythmia in SCD.[4] In fact, around 50% of SCD cases are due to VF and/or ventricular tachycardia (VT).[3] They predominantly occur out-of-hospital, explaining the low survival rates (i.e., <10%) of patients with VF.[5] Conversely, asystole and pulseless electrical activity (PEA) have been emerging in SCD for indefinite reasons.[3] Interestingly, in patients with reported out-of-hospital sudden cardiac arrest (SCA), antipsychotic drugs have shown to be significant predictors of PEA versus VF/VT.[6]

SCD can be caused by an acquired and/or a genetic background of susceptibility, arising from either electrophysiological (e.g., inherited channelopathies) or structural cardiac abnormalities (e.g., CAD).[1]

Inherited channelopathies

Long QT syndrome (LQTS), Brugada syndrome (BrS) and short QT syndrome (SQTS) are rare inherited arrhythmia disorders arising from ion channel abnormalities, which in turn are termed channelopathies. These syndromes are highly concerning, particularly in young people, due to their high propensity to suffer severe ventricular arrhythmias and sudden cardiac death.[7]

Since the overwhelming majority of patients with inherited channelopathies have no structural heart diseases, an electrocardiogram (ECG) is a valuable tool both in detecting features of these syndromes and in early SCD risk stratification.[1,7]

QT prolongation, torsades de pointes and congenital long QT syndrome

The QT interval represents the electrocardiographic index of ventricular repolarization and depolarization.[8] Because the QT interval varies inversely with heart rate, several correction formulas (e.g., Bazett, Fridericia) allow us to determine a heart rate-corrected QT (QTc) interval. Fridericia's formula provides a more accurate assessment at extremes of heart rate than Bazett's formula and, therefore, it is preferred in such cases.[9,10]

The expert group from the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) gives an upper limit of normal (i.e., estimated 99th percentile) for abnormally prolonged QTc intervals of 470 ms and 480 ms in otherwise healthy post-pubertal males and females, respectively.[11] Patients with an absolute QTc interval of >500 ms are considered to be at risk for

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