Cardiac arrhythmias related to psychiatric medication

A brief review

M. Elsayed; R. W. Freudenmann; C. Schönfeldt-Lecuona; B. J. Connemann; M. Gahr

Klinik für Psychiatrie und Psychotherapie III, Universitätsklinikum Ulm

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Keywords

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Zusammenfassung

Diese narrative Übersichtsarbeit fasst das Wissen über kardiale Arrhythmien (z. B. QT-Zeit-Verlängerung, Torsade de pointes Tachykardie TdP, plötzliche Herztod) unter Psychopharmaka zusammen. Unter den gebräuchlichsten Antipsychotika sind Amisulprid und Ziprasidon am häufigsten mit TdP assoziiert. Die Behandlung mit einigen Antidepressiva (SSRIs, trizyklische Antidepressiva) ist mit einer 5- bis 6-fachen Erhöhung der Inzidenz von ambulanten Herzstillständen assoziiert. Lithiumtherapie ist mit Bradykardie, T-Wellen-Veränderungen und AV-Block assoziiert. Anxiolytika vom Typ der Benzodiazepine zeigen meist keine kardialen Nebenwirkungen. Besonders kardial risikoreich hingegen ist die Kombination von mehreren Medikamenten (auch Nichtpsychopharmaka), die die QT-Zeit verlängern.

Summary

This narrative review summarizes current available information about cardiac arrhythmias (QT prolongation, Torsade de pointes Tachycardia [TdP], sudden cardiac death) associated with psychiatric medication. Among the most commonly used antipsychotics, amisulpride and ziprasidone are most frequently associated with TdP. Treatment with some antidepressants (SSRIs, tricyclic antidepressants) is associated with a 5- to 6-fold increase in the incidence of out-of-hospital cardiac arrest. Lithium is associated with bradycardia, T-wave changes and AV-block; anxiolytics of the benzodiazepine group do usually not have cardiac side effects. The combination of multiple drugs (including medications from general medicine) that prolong the QT interval has a particularly high cardiac risk.

Korrespondenzadresse

Mohamed Elsayed
Klinik für Psychiatrie und Psychotherapie III
Universitätsklinikum Ulm
Leimgrubenweg 12–14, 89073 Ulm
Mohamed.Elsayed@uni-ulm.de

Kardiale Arrhythmien im Zusammenhang mit Pharmakotherapie – Eine kurze Übersicht
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Psychiatric medication (PM) is essential in the treatment of many mental disorders such as schizophrenia and affective disorders etc. (1). The most commonly used substance classes are antipsychotics, antidepressants such as tricyclic anti-depressants (TCA), selective serotonine reuptake inhibitors (SSRI), mood stabilizers, anxiolytic agents such as benzodiazepines and hypnotics such as antihistaminics or benzodiazepine analogues (2). PM is associated with different adverse drug reactions (ADR) that are more or less typical for each substance and substance group (3). One of the most common ADR associated with PM are cardiac side effects. They range from simple tachycardia, supraventricular and ventricular arrhythmias, over myo(peri)carditis and cardiomyopathy to fatalities due to cardiac arrest (4). A large body of literature suggests that mortality is increased in psychiatric patients compared to the general population even after excluding suicides (5, 6). This increase has been explained by a higher mortality due to fatal arrhythmias (formerly referred to as sudden (cardiac) death, SCD), and it has in part been attributed to negative life style factors like more smoking, poor use of preventive medicine (7) and genetic changes involve for both psychiatric and cardiac disease (8). In addition, many patients treated with PM are elderly and therefore, have a high risk of all forms of heart disease (9) including SCD. They must be considered to be a high-risk group when exposed to drugs with pro-arrhythmic potential. In recent years, there has been an increasing concern about the cardiac risk profile of PM. Electrocardiographic changes due to PM include prolongation of the PQ-Interval, atrioventricular blocks of different degrees of severity, widening of the QRS interval (bundle branch block), ST-segment changes (repolarization disturbances), and prolongation of the QT interval. When psychotropic substances are developed, tested and approved for their use in clinical psychiatry, the new drugs are rigorously tested for their cardiovascular risk profile, particularly concerning their risk of causing a prolonged QT interval in recent years (10).

The brief review article will discuss mechanisms of drug-induced prolongation of the QT-interval and psychotropic drugs in regard of their risk of inducing prolongation of the QT interval.

Basic aspects

It is commonly accepted that a prolongation of the QTc interval is associated

with the risk of Torsades de Pointes (TdP) tachycardia which, in turn, can lead to ventricular fibrillation (VF) and SCD. TdP was first described in 1966 by French cardiologist François Dessertenne. It can be recognized on the electrocardiogram (ECG) as a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line. TdP clinically results in malaise, syncope, and cardiac death via ventricular fibrillation. A prolongation of the QTc interval is an important surrogate parameter for the risk of developing TdP because it is measureable. The QT interval is considered the traditional measurement for assessing the duration of ventricular de- and repolarization. The QT Interval is measured in milliseconds (ms) on the body surface electrocardiogram (ECG) from the Q-top, the beginning of the QRS complex, until the end of the T wave, and should be corrected for heart rate to enable comparison with reference values. For men, the cut-off points are less than 430 ms (normal), 430–450 ms (borderline) and more than 450 ms (prolonged), and, for women, less than 450 ms (normal), 450–470 ms (borderline), and more than 470 ms (prolonged) (11). Several methods are used to adjust for the effect of heart rate (e.g. Fridericia formula: QT-time/RR-period Bazett´s formula QT-time/√RR-period).

Drug-induced prolongation of the QT interval and genetic long QT syndrome

Risk factors for the prolongation of the QT interval and the generation of TdPs may be extra-cardiac-, cardiac- and drug-related. Drug-induced TdPs mainly develop, if two or more drugs with this risk are combined. The presence of one or several additional risk factors, e.g. hypokalemia, requires ECG recording prior to treatment with psychotropic drugs, especially when the intravenous route is used (12). The mechanisms for both the prolongation of the QT interval and its associations with TdP, VF and SDC, however, are not fully understood. The current model is that medications including psychotropic drugs can prolong the QT interval by blocking the human ether-à-go-go-related gene (hERG) potassium channel. This interferes with proper repolarization of the myocard and, therefore, increases the vulnerability for fatal arrhythmias (13). Examination of in vitro models including heterologous expression systems showed that the equilibrium between inward and outward currents across the cell membrane plays an important role in controlling the duration of the action potential in the ventricular myocyte. The disturbance of the normal balance between inward (depolarizing) and outward (repolarizing) currents as well as the increase in depolarizing current, or alternatively, the decrease in repolarizing current carried by potassium (K+) ions is implicated with QT prolongation (14–16).

Many psychotropic drugs block several potassium currents (eg, Iks and Ikr) during repolarization (phases 2 and 3 during the action potential), resulting in a prolonged QT interval on the ECG with an increased risk of developing TdP. Drugs such as methadone, amitriptyline, haloperidol, and sertindole promote QT prolongation by blocking the hERG potassium channels (17, 18). In addition, eight phenotypes of the congenital long QT syndrome are recognized. The most frequent phenotypes for potassium channels are KCNQ1 (or KVLQT1) coding long QT type 1 (LQT1) and KCNH2 coding LQT2; for sodium channels, SCN5A is responsible for the LQT3 phenotype. Torsade de Pointes may also present as palpitations, dizziness, or syncope. Drug-induced QT-interval prolongation is most often due to a dose dependent inhibition of the cellular Ikr current through channels coded by the hERG gene (18).

Antipsychotics

Antipsychotics may cause significant cardiac side effects by affecting cardiac conduction. They can cause prolongation of the QT interval (19, 20). First generation antipsychotics such as haloperidol, thioridazine, sertindole, pimozide, droperidol, as well as second-generation AP, such as quetiapine, risperidone, olanzapine, iloperidone, and most markedly ziprasidone and amisulpride have been associated with QT prolongation in clinical studies, meta-analyses and and case reports (20, 21). An analysis of 1665 spontaneous reports of TdP cases to the FDA's Adverse Event Reporting System (AERS) (2004–2007) revealed that the antipsychotic drugs most commonly associated with TdP were ziprasidone (28 cases), haloperidol (22), risperidone (23) and quetiapine (24).

A particular issue is sertindole. This second-generation antipsychotic has been withdrawn from the market soon after its launch in the 1990s because of its potential to prolong the QT interval. The substance is now marketed again, but only as a second-line substance and its use requires a number of mandatory measures to minimize risk (e.g. QT measurements before and under treatment, control of serum potassium levels). If used, physicians should carefully adhere to the recommendations of the manufacturers provided in the Summary of Product Characteristics (SmPC).

After a first warning from the U.S. Food and Drug Administration (FDA) in 2007, the German manufacturer (Janssen-Cilag) no longer recommended the intravenous application of haloperidol as of 2010, and only supported intramuscular injections. The manufacturer had concerns that continuous cardiac monitoring to detect QTc prolongation and all its sequelae is not performed as required, which was certainly true for most psychiatric settings. If cardiac monitoring is performed (e.g. on intensive care units), intravenous application is still allowed. But even if used orally, patients treated with haloperidol should undergo ECG controls.

Antidepressants

Antidepressants have many cardiovascular side effects including tachycardia, hyper- and hypotension, ECG changes, electrolyte abnormalities, reduced cardiac conduction and output, arrhythmias, and SCD (4). Different categories of antidepressants, particularly TCAs, provoke various types of arrhythmias through complex processes at voltage-gated sodium, potassium, and calcium ion channels in cardiac myocytes and the conduction system (25–27). Of note, the results of a recently published large-scale epidemiological study estimated the risk of SCD and ventricular arrhythmia to

be 3.3/1000 person-years after antidepressant exposure (28). Weeke et al. showed that treatment with SSRIs and TCAs was associated with up to a 5- to 6-fold increase in the incidence of out-of-hospital cardiac arrest (29). On the other hand, untreated depression per se more than doubles the risk of SCD which adds to the overall risk of SCD in these patients (30).

The approval studies for the venlafaxine and duloxetine, which are among the most commonly prescribed antidepressants, showed that the therapeutic doses of these drugs were not associated with changes of the QTc interval. Lower level evidence from case reports, however, suggests that QTc prolongation can arise under treatment with fluoxetine, citalopram, or venlafaxine at toxic doses, or when multiple additional risk factors are present (31–33).

Mood stabilizers

Carbamazepine, lamotrigine, valproate, and lithium are used as mood stabilizers, most prominently in bipolar affective disorders. The anti-convulsive drugs have generally not been associated with severe arrhythmia (34). Caution should be taken, however, in patients treated concomitantly with anti-arrhythmic drugs (35). Regarding a QT prolonging effect of lithium, reports are divergent (10, 34, 36, 37), but bradycardia, T-wave changes and AV-block have been described (38). Lithium in concentrations above 1.2 mmol/L can markedly prolong the QTc interval (35).

Medications

Treatment of opioid addiction

Methadone causes pronounced QT prolongation (35) and several cases of TdP have been reported. The Substance Abuse & Mental Health Services Administration (SAMHSA) has proposed a cardiac risk management plan for methadone maintenance treatment programs (17). SAMHSA recommends that a baseline ECG should be recorded if the patient has risk factors and that ECGs for such patients should be recorded annually or when the daily dose exceeds 120 mg. However, both methadone dose and baseline QT length are predictors of QT prolongation (10, 39). Thus, we recommend baseline and follow-up ECG's, including an additional evaluation if the daily dosage exceeds 100 mg, as recommended in the guideline by Krantz et al (40). Compared with methadone, the buprenorphine causes far less prolongation of the QT interval (49) and TdP has not been reported.

Treatment of alcohol dependence

Acamprosate is a well-tolerated substance used for treating alcohol dependence. A number of randomized, controlled trials have evaluated the effectiveness of naltrexone in the management of alcohol dependence. Both substances were not associated with a risk of developing arrhythmias.

Anxiolytics

Benzodiazepines and pregabalin are widely used in treatment of various anxiety disorders. Benzodiazepines comprise a heterogeneous group of drugs. In vitro studies have shown both inhibition and activation of potassium currents during exposure to benzodiazepines (42–43) but no changes in QT duration have been reported in clinical use (43). Buspirone is an anxiolytic drug available for oral administration with well-established safety, it is used for the treatment of depression and anxiety disorders. Opipramol is a sigma receptor agonist and has a broad spectrum of anxiolytic activity. No significant cardiac ADR related to opipramol are described in the literature or in the summaries of product characteristics.

Discussion

Drug-induced long QT syndrome still is an important safety problem related to psychiatric medication. Some antipsychotics such as thioridazine, pimozide are not longer recommended because of its QT prolonging properties. Other PMs make careful monitoring of the QTc interval inevitable (e.g. sertindole with is restricted labeling, amisulprid, ziprasidone, haloperidol, quetiapine, citalopram, methadone). This situation can be compared to general medicine where some substances have this risk (e.g. amiodarone and sotalole, quinidine, chloroquine, chinolone and macrolide antibiotics, azole antifungal medications, propofole and sevoflurane anesthetics) and others have been withdrawn from the market because of a high risk of QTc prolongation and fatal arrhythmias (cisapride, fenflumarine, astemizole, terfenadine and bepridil).

Morbidity and mortality associated with a prolongation of the QT interval currently constitute the most frequent cause of drug withdrawal from the market or "black-box" warning after marketing (50). Given the vast number of psychiatric and other medications that have been associated with different risks of causing cardiac arrhythmias of different severity many clinicians use summaries and lists in handbooks, websites and apps for smart phones today. They can quickly provide an overview of the most dangerous substances, and also help detecting dangerous interactions in case of multiple pharmacological agents. Examples are QTdrugs.org/www.torsages.org which are now available from www.CredibleMeds.org after registration.

Open questions and future research options

Despite the available data about cardiac side effects of psychotropic medication more randomized clinical trials are needed to provide physicians more information about substances with lower cardiac risk. Understanding the exact mechanism of QT prolongation and Torsade de points Tachycardia (TdP) in the future could help to decrease mortality due to medication side effects.

Conflict of interest

No conflict of interest.

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