Med Clin (Barc). 2015;144(6):269–274

MEDICINA CLINICA

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Review

# Drug-induced QT interval prolongation: Do we know the risks?☆

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ARTICLE INFO

*Article history:*
Received 29 October 2013
Accepted 30 January 2014
Available online 21 November 2015

*Keywords:*
QT interval prolongation
*Torsade de pointes*
Drugs
Risk factors
Drug interactions

ABSTRACT

Sudden cardiac death is an important cause of mortality in developed countries, most of them being consequence of acute ventricular arrhythmias. These arrhythmias, in some cases, owe to QT interval prolongation.

A major risk factor for this condition is the use of drugs that prolong the QT interval. In fact, in recent years, one of the most common reasons for drug withdrawal or usage restrictions has been drug induced QT interval prolongation that involves both cardiovascular and non-cardiovascular drugs.

Taking into account the severity that the occurrence of such an event may have, it is important for clinicians to know the risks of these drugs in certain patients. In this review we analyse the drugs that prolong the QT interval, the risk factors that can enhance QT prolongation and the drug interactions that can increase these risks.



## Prolongación del intervalo QT inducido por fármacos: ¿conocemos sus riesgos?

*Palabras clave:*
Prolongación del intervalo QT
*Torsade de pointes*
Fármacos
Factores de riesgo
Interacciones farmacológicas

RESUMEN

La muerte súbita cardiaca es una causa importante de mortalidad en los países desarrollados. La mayoría de ellas derivan de arritmias ventriculares agudas que, en algunas ocasiones, se producen como consecuencia de la prolongación del intervalo QT.

Un importante factor de riesgo para esta alteración es el uso de fármacos que prolongan este intervalo. De hecho, en los últimos años, uno de los motivos más frecuentes de retirada del mercado de medicamentos o de restricciones de uso ha sido la prolongación del intervalo QT, e implica tanto fármacos cardiovasculares como no cardiovasculares.

Dada la gravedad que puede conllevar la aparición de un suceso por esta causa, es importante que los clínicos conozcan los riegos del uso de estos fármacos en determinados pacientes. En esta revisión analizamos los fármacos que prolongan el intervalo QT, los factores de riesgo que pueden influir y las combinaciones de fármacos que pueden agravar esta situación.



## Introduction

Currently, sudden cardiac death (SCD) is an important public health issue in developed countries. Approximately 12% of natural deaths occur suddenly; of these, 88% are due to cardiac problems, which is the cause of death of more than 50% of the patients with coronary heart disease.[1,2] Most SCD cases are caused by acute ventricular arrhythmias (80–85%) and are due to coronary disease.[3] However, they are sometimes caused by arrhythmias as a consequence of the prolongation of the QT interval.[4,5]

A significant risk factor for these disorders is the use of QT-prolonging drugs.[6] In fact, in recent years, one of the most frequent reasons for withdrawing drugs from the market or restricting their use has been the prolongation of the QT interval. This is because, despite their low prevalence, it is well known that severe episodes due to this cause may lead to deadly consequences.[6,7] Nowadays, the prolongation of the QT interval with or without related proarrhythmic effect is, together with the hepatotoxicity, the most common cause for the withdrawal of commercialised drugs.[8,9]

☆ Please cite this article as: Villamañán E, Armada E, Ruano M. Prolongación del intervalo QT inducido por fármacos: ¿conocemos sus riesgos? Med Clin (Barc). 2015;144:269–274.

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2387-0206/

It is important for clinicians to know the risks involved in the use of these drugs in certain patients.[8] Generally, this risk is considered when prescribing antiarrhythmic drugs, although not only these agents have this effect. There are several non-cardiovascular drugs that may potentially prolong the QT interval and worsen or provoke *torsade de pointes* (TdP). This possibility is even higher in patients with other associated factors, such as comorbidity, advanced age, liver or kidney failure, baseline cardiac disease or electrolytic alterations and, in addition, patients who frequently receive intravenous drugs. At the same time, some QT-prolonging drugs can modify heart rate (HR), which, together with certain clinical situations that can also affect HR, further complicate QT variations and their consequences.[8]

Currently, several regulatory agencies require identifying possible risk for QT interval prolongation before and after the authorisation of drugs. In 2005, the European Medicines Agency (EMA) published a document with recommendations for the assessment of QT interval prolongation and the proarrhythmic potential for non-antiarrhythmic drugs. Since then, these guidelines are an essential requirement in the authorisation process of new drugs in Europe.[10] That year, the U.S. Food and Drug Administration (FDA) published guidelines addressed to the industry, with rules for the clinical evaluation of QT/QTc (corrected QT) interval prolongation before the commercialisation of a drug in USA.[11]

In light of the above, it is important for clinicians to be aware of the risks involved with the use of these drugs in certain patients. In this review, we will analyse QT-prolonging drugs, risk factors that may increase the possibilities of TdP and drug combinations that could exacerbate this situation.

## Drugs that prolong the QT interval and may cause *torsades de pointes*

The relationship between certain drug treatments and the prolongation of the QT interval has long been known. The appearance of syncopes related to the beginning of the treatment with quinidine was observed for the first time in the 1920s. In the 1960s, a "pause-dependent" polymorphic ventricular tachycardia was identified as an underlying mechanism.[12] In 1966, the term *torsade de pointes* was conceived to describe a specific ventricular tachycardia detected in elderly women with heart block.[13]

Nevertheless, despite the clinical importance of the lengthening of the QT interval and the correlation with certain drugs in its incidence, contrary to expectations, published studies are scarce. Also, this lack of data means that there is not enough information regarding the number of hospitalised patients with prolonged QT, the frequency by which patients who are prescribed QT-prolonging drugs develop long QT syndrome or TdP, or a clear consensus about the degree of prolongation required to suspend treatment QT-prolonging drugs.

As for drugs commercialised after 2005, information about their impact on QT interval derives from clinical trials because, as previously stated, this is required by regulatory agencies before their commercialisation. Meanwhile, due to the lack of regulations, information regarding old drugs derives from a series of non-controlled cases.

Regarding already commercialised drugs, the following is a description of the main drug groups that potentially affect the QT interval.

### *Antiarrhythmic drugs*

This is the only drug group for which there is information available about its association with QT interval and TdP.[14] As per this data, the incidence of TdP for antiarrhythmic sodium and potassium channel blockers, such as quinidine, disopyramide and procainamide, as well as those that only block potassium channels, such as sotalol, is between 1 and 10%.[14]

It is important to highlight that, while class Ia antiarrhythmic drugs are clearly related with the appearance of TdP, their association with class III is not that clear. Thus, according to what was deduced from the results of 17 studies that included 2878 patients between 1982 and 1993, the incidence of TdP with amiodarone is only 0.7%.[15] This incidence is higher in women and patients with renal failure or congestive heart failure, among others.

### *Antihistamines*

Within this drug group, the lengthening of the QT interval has been observed for some of the second generation antihistamines (mainly terfenadine). Some resulted in TdP,[16] although these cases occurred because of doses that exceeded recommended amounts or regular doses that were administered together with cytochrome P450 inhibitors, or in patients with liver failure. Non-sedating or third generation antihistamines, such as loratadine, cetirizine or ebastine (most recently commercialised) have not been related to QT prolongation or TdP.[17]

### *Antimicrobial drugs*

#### *Antibiotics*

The association of arrhythmias related to QT interval prolongation with antibiotics is not very frequent. Moreover, the known cases were due to macrolide and fluoroquinolone use.[18,19] Among the macrolides, erythromycin and clarithromycin have been related to ventricular arrhythmias[14,20–23] and SCD.[24,25] The treatment with azithromycin has also been related to TdP cases.[26] Moreover, an important retrospective study published in 2012 with an extensive patient sample demonstrated that, after 5 days of treatment with this drug, there was an increase in deaths due to cardiovascular causes compared with people treated with amoxicillin, ciprofloxacin or no treatment. In addition, the risk was even higher in some cases, such as in patients with baseline cardiovascular disease or those who presented prolonged QT intervals.[27] In light of these results, both the FDA as well as the EMA sent security alerts about this risk associated with the use of azithromycin.

The second group of antibiotics that affect the QT interval is made up of fluoroquinolones. This is a class effect, even though there are differences between them. In the previously mentioned study, levofloxacin demonstrated a risk of cardiovascular death similar to azithromycin. Thus, it would not be an alternative to the use of macrolides in this type of patients. Among them, ciprofloxacin seems to be the safest.[18] Furthermore, the available information reveals that 24% of TdP cases associated with fluoroquinolones took place when other drugs that prolong the QT interval were administrated, 62% in patients with baseline cardiac disease, 7% in patients with renal failure and 17% in patients with hypokalaemia or hypomagnesaemia, and 67% in women.[18,23]

#### *Antifungal medicines*

Ketoconazole, itraconazole, fluconazole and voriconazole have been associated with cases of long QT and appearance of TdP. Ketoconazole and itraconazole prolong the QT interval by blocking potassium channels. However, most reported cases were due to a co-administration with other QT-prolonging drugs that metabolise the same way. This is because they are inhibitors of cytochrome P450 isoform 3 A4.[17,18]

#### *Antimalarial drugs*

This group of drugs deserves special attention. Quinine and quinidine have been shown to prolong QT at regular doses. In