The risk of treatment-induced QT interval prolongation

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Abstract

Objective: QT interval prolongation can increase patients’ hospital stay and mortality rate. This study aims to determine the incidence of drug-induced QT interval prolongation and establish which QT interval measurement method is the most appropriate for electrocardiographic monitoring.

Method: A retrospective observational study was conducted of patients admitted to the Clínica Bíblica Hospital during 2018. The electronic medical records of patients hospitalized for longer than 48 hours and whose drug regimen included at least one drug potentially able to prolong the QT interval were reviewed. Manually-measured QT intervals were corrected using Fridericia’s and Rautaharju’s formulae, while automatically-measured QT intervals were corrected with Bazett’s formula. Risk was assessed using the RISQ-PATH scale.

Results: Of the 141 patients analyzed, 23 had arrhythmia as per their clinical history and 14 suffered a complication during their stay in hospital. A total of 113 (80%) had a high RISQ-PATH score and only 64 were sub-

PALABRAS CLAVE

Intervalo QT prolongado; Farmacia clínica; Farmacia hospitalaria; Medicina cardiovascular.

KEYWORDS

Prolonged QT interval; Clinical pharmacy services; Hospital Pharmacy Service; Cardiovascular agents.
Conclusions: Es necesario implementar estrategias que permitan una mejor monitorización del intervalo QT con el fin de prevenir las complicaciones derivadas en las pacientes hospitalizadas.

Methods
A retrospective observational study was carried out of patients admitted to the Clínica Bíblica Hospital, a 78-bed private center located in San José, Costa Rica.

An analysis was conducted of the clinical records of all patients over 18 years of age hospitalized for over 48 hours and administered at least one drug from list 1 (medicines associated with QT interval prolongation) or two or more drugs from lists 2 and 3 of the CredibleMeds classification. These lists enumerate medicines capable of prolonging the QT interval that are clearly associated with TdP (list 1); medicines capable of prolonging the QT interval but where an association with TdP has not been demonstrated (list 2); and drugs that have been shown to result in TdP only under certain conditions (list 3) such as the administration of excessive doses, hypokalemia, concomitant use of drugs inhibiting the metabolism of QT interval prolonging medicines, and TdP-inducing electrolytic disorders.

Patients with pacemakers and those whose clinical records lacked the information minimally required for our analysis were excluded from the study. Data was gathered both from the patients’ electronic medical records and from paper-based records by a group of pharmacy students supervised by their professors and by clinical pharmacists. The MPH Hospitalized Patients Management System, the SIH Integrated Hospital Management System and the SFPA Pharmacy System were reviewed.

The following information was obtained: (1) general characteristics (age, sex, diagnosis on admission, length of hospital stay), (2) drugs associated to QT interval prolongation (active ingredient, route, dose), (3) existing drug-drug interactions, (4) clinical factors associated to QT interval prolongation (RISQ-PATH score), (5) electrocardiographic data (ECC result, QTc value obtained manually or automatically), among others and (5) management in the event of arrhythmias and electrocardiographic disorders. The RISQ-PATH score was used with a cutoff value of 10 points. Patients with higher scores were classified as patients at a high risk of suffering QT interval prolongation during their stay in hospital. The assessment of risk was carried out using the RISQ-PATH scale.

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The medicines associated with an increased risk of QT interval prolongation, and which were prescribed to hospitalized patients included levosulpiride (58%), ondansetron (56%), amiodarone (19%), metronidazole (8%) and fluconazole, which are clearly connected to the risk of torsade de pointes tachycardia, particularly if they are used in patients with additional risk factors.

Several procedures have been developed to prevent QT interval prolongation, which are based on drug therapy, potentially correctable factors and structural diseases or hereditary genetic arrhythmias. When a prolonged QT interval is detected, the patient must be evaluated and all the medicines in their drug regimen able to prolong the QT interval must be discontinued. The reduction of the incidence of QT interval prolongation at hospital level requires pharmacotherapeutic and electrocardiographic monitoring and an assessment of the risk factors presented by each patient. Implementation of a protocol aimed at preventing QT interval prolongation and the complications associated to it is also necessary.

This study seeks to determine the incidence of patients at risk of presenting with treatment-associated QT interval prolongation in a private hospital in Costa Rica, evaluate the drugs prescribed to treat the condition and the most common clinical risk factors faced by patients. Moreover, an analysis was made to determine which QT interval measurement method (manual or automatic) and which of the available adjustment or correction formulae (QTc) are best suited to electrocardiographically monitor hospitalized patients.

Results
Between January and December 2018, a total of 540 patients were admitted to the Clínica Bíblica Hospital, of whom 141 fulfilled the inclusion criteria. Of them, 30 (21.2%) were either currently affected by some kind of arrhythmia or electrocardiographic disorder (17, 12%) or had experienced such conditions in the past (23, 16.3%). Fourteen of the latter (9.9%) experienced a complication of their arrhythmia during their stay in hospital. Electrocardiographic disorders included atrial fibrillation, left branch bundle block, extrasystole, trigeminy and a side effect potentially associated with the use of digoxin. The characteristics of patients included in the study can be seen in table 1.

Of the total of high-risk patients (113), only 64 (56.5%) were subjected to an ECG on being admitted to the hospital. For 25 (39.0%) of them, at least one follow-up ECG was found which allowed a comparison of the QT interval before and after indication of a pharmacological therapy. In this population, it was found that 10 (15.6%) patients presented with a delta QT value (difference between the follow-up QT and the QT on admission) of ≥ 30 ms. Four of these patients (40%) exhibited a difference of over 60 ms, which is considered a severe QT interval prolongation, denoting a much higher risk of experiencing life-threatening cardiac events.

On the other hand, 62 (54.8%) of the 113 patients were considered high-risk even before being treated in hospital; 22 (35.5%) of them presented with QT interval prolongation during their stay in hospital and in 5 (8.0%) of them the risk was associated with the use of such drugs as quinolones (maxifloxacin and ciprofloxacin) and fluconazole, which are clearly connected to the development of TdP.

A comparison of the manual measurement of the QT interval with the values provided by electrocardiography showed a significant difference between both (p = 0.0004). The corrected QT interval (QTc) obtained using both methods were also compared, with manually obtained values being superior to automatically-obtained ones.

Conclusions: Every effort should be made to implement strategies conducive to more effective monitoring of the QT interval to prevent QT interval prolongation related complications in hospitalized patients.

Introduction
QT interval prolongation may result in a lengthening of the patients’ hospital stay and in an increase in morbidity and mortality. Moreover, many drugs are available which are able to prolong the QT interval and increase the risk of torsade de pointes (TdP) tachycardia, particularly if they are used in patients with additional risk factors.

Several procedures have been developed to prevent QT interval prolongation, which are based on drug therapy, potentially correctable factors and structural diseases or hereditary genetic arrhythmias. When a prolonged QT interval is detected, the patient must be evaluated and all the medicines in their drug regimen able to prolong the QT interval must be discontinued. The reduction of the incidence of QT interval prolongation at hospital level requires pharmacotherapeutic and electrocardiographic monitoring and an assessment of the risk factors presented by each patient. Implementation of a protocol aimed at preventing QT interval prolongation and the complications associated to it is also necessary.

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When corrected using Bazett’s formula, QTc intervals were longer than when Rautaharju’s formula was used (p ≤ 0.0001). No significant difference was found between corrections with the Bazett and the Fridericia formulas, but a significant difference was observed between corrections made with the Fridericia’s formula and those where Rautaharju’s formula was used (p ≤ 0.0001).

**Discussion**

QT interval prolongation tends to be closely connected with the appearance of ventricular arrhythmias such as TdP, which could even result in sudden death. Similarly, this electrocardiographic alteration has been associated with longer hospital stays and to increased mortality due to cardiovascular events. When corrected using Bazett’s formula, QTc intervals were longer than when Rautaharju’s formula was used (p ≤ 0.0001). No significant difference was found between corrections with the Bazett and the Fridericia formulas, but a significant difference was observed between corrections made with the Fridericia’s formula and those where Rautaharju’s formula was used (p ≤ 0.0001).

The incidence of QT interval prolongation is generally high among hospitalized patients. In an analysis of 422 elderly adult hospitalized patients, the alteration was identified in 32% of cases, while another study conducted at the emergency room of a third-level hospital, 95 (34.1%) of 279 patients were found to have a high QT interval prolongation risk before their admission, i.e. prior to their therapy being prescribed. This shows the importance of identifying patients at risk as early as possible.

Several studies have shown that the likelihood of developing TdP as a result of administration of drugs that increase the risk of QT interval prolongation is significantly higher in hospitalized patients. This can be explained by the fact that this patient population tends to be older than average, which was the case of the patients in this study, where mean age was 66 years. Moreover, this kind of patient usually presents with additional risk factors such as electrolytic disorders and hepatic and renal dysfunction.

Hypokalemia is a risk factor that was observed in 10% of the patients analyzed. The presence of hypokalemia on admission by itself trebles the risk of QT interval prolongation. Only half of the patients in this study were subjected to an ECG on admission, two of them presenting with a prolonged QT interval of 450 and 606 ms.

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Different analyses have pointed out that, because of the long list of drugs associated with a risk of QT interval prolongation, electrocardiographic monitoring is not feasible in all patients treated with these drugs. However, in patients presenting with some kind of arrhythmia during their hospital stay, or in those with multiple risk factors, such monitoring should be performed in all cases as it is considered to be the most efficient way of preventing adverse events.

The use of more than one QT interval prolonging drug is a risk factor. In a recent study, 48% QT interval prolongation events were attributable to the use of more than one QT interval prolonging drug.
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to the medication and involved two or more high risk medicines in 25% of cases22,28. The high number of drugs that were on average prescribed to the patients in this study could be related to the observed incidence of QT interval prolongation. At any event, other treatment alternatives should be evaluated.

Another factor that should be borne in mind when prescribing QT interval prolonging medicines is the relationship between the drugs' plasma concentration and the effect this concentration has on risk. Fourteen patients (12%) of the sample analyzed presented with clearance rates below 30 mL/min, with three patients being prescribed higher doses than recommended or required as a function of the patients' glomerular filtration rate27.

Measurements of the QT interval were made both manually and automatically. The latter methods are not always accurate and require manual validation of the results obtained, particularly in patients with electrocardiographic abnormalities such as early repolarization and arrhythmia (including atrial fibrillation)21,22.

Another limitation associated with automatic determination of the QT interval has to do with correcting potential prolongations. Indeed, even if the most commonly used method is Bazett’s formula, previous studies have questioned the value of this method, suggesting that Fridericia’s method should be the correction method of choice11. The shortcomings of Bazett’s formula have been extensively documented in other studies. It is to be expected for some formulae to be more appropriate than others depending on specific characteristics of the studied population such as their heart rate, their sex, their ethnicity, and their age20.

In patients with a QRS complex ≥ 120 ms, it was deemed necessary to use Rautaharju’s formula to correct the QT interval as a statistically significant difference was observed between Rautaharju’s formula and Bazett’s and Fridericia’s formulae. This could be attributable to the fact that Rautaharju’s is the only formula that takes heart rate fluctuations into consideration when making the correction13,14.

The fact that this is a descriptive study conducted in a retrospective manner based on the analysis of clinical records constitutes a limitation as the sample analyzed presented with clearance rates below 30 mL/min, with three patients being prescribed higher doses than recommended or required as a function of the patients’ glomerular filtration rate27.

The results obtained from this study indicate that the risk of drug-induced QT interval prolongation is fairly common, making it necessary to implement strategies conducive to more effectively monitoring and correcting the QT interval (QTc) in order to prevent the complications associated with prolongation. Every effort should be made to mitigate preventable risk factors avoiding QT interval prolonging drugs, excessive dosing of high-risk drugs or abnormal electrolyte levels.

In addition, institutional protocols must be implemented that promote ECG-based monitoring of patients at risk or who suffer from diseases associated to electrocardiographic disorders as the onset of TdP and other ventricular tachyarrhythmias may be prevented if a growing QT interval is detected on time20,21,25.

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Conflict of interest

No conflict of interest.

Contribution to the scientific literature

The present study provides the reader with an idea of the great importance of QT interval monitoring and of the development of a protocol aimed at appropriately managing patients at risk of QT interval prolongation during their hospital stay. It must be taken into consideration that over 50% of patients in the study already exhibited risk factors at the time of admission and 56% received at least one drug previously shown to increase the QT interval prolongation risk.

The study emphasizes the need of implementing a QT interval monitoring strategy at the Clínica Bíblica Hospital to reduce complications and shorten the patients’ length of hospitalization.

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