ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Comparison of Corrected QT and Tp-e/QTc Interval in Intoxication with Drugs That Cause QT Prolongation in Children

Çocuklarda QT Uzaması Yapan İlaçlarla Zehirlenmelerde Düzeltilmiş QT ve Tp-e/QTc Süreleri Karşılaştırması

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Abstract

Introduction: Childhood intoxications are among the most common reasons for admission to the emergency department. The aim of this study is to evaluate whether there is a primary marker that can determine the risk of arrhythmia by comparison of QT, QTc, QT/QTc, Tp-e/QT, Tp-e/QTc intervals in drug intoxications with prolonging QTc which can be fatal by causing arrhythmia in children.

Materials and Methods: In this study, 55 patients who were admitted to Pediatric Emergency Department of Training and Research Hospital between January 2018 and August 2019 within the first 6 hours due to intoxication with QTc prolongation and followed up in our pediatric emergency department were retrospectively reviewed. In patients hospital records, age, sex, medication, time of application, clinical and physical examination findings, vital signs, treatments and results, laboratory findings, electrocardiogram findings at the time of admission hospital and in the 6. hour control, QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc times were recorded.

Results: The median age of the patients in study was 155±77.2 months. The number of female patients was 33 (60%) and the number of male patients was 22. There was a statistically significant difference between leukocyte count, hemoglobin, platelet,bun, creatinine, SGPT and calcium values at the time of admission and control at the 6th hour. There was no statistically significant difference between CK-MB and troponin levels. Also, there was no statistically significant difference between QT, QTc, QT/QTc, Tp-e/QT and Tp-e/QTc intervals. But there was a statistically significant difference between Tp-e/QTc ratio and gender.

Conclusions: Although QTc interval continues to be used to determine the risk of arrhythmia in children with drugs prolonging QTc, it may be significant to compare Tp-e and Tp-e/QTc ratio. However, studies involving a larger number of patients are needed to determine whether Tp-e interval and Tp-e/QTc ratio are a priority marker.

Keywords
Children, intoxication, Tp-e/QTc ratio

Anahtar kelimeler
Çocuk, zehirlenme, Tp-e/QTc oranı

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Öz

Giriş: Çocukluk çağı zehirlenmeleri sık görülen acile başvuru nedenleri arasındadır. Bu çalışmada amacımız aritmiye neden olarak ölümcül olabilecek QTc uzaması yapan ilaçlarla zehirlenmelerde QT, QTc, QT/QTc, Tp-e/QT, Tp-e/QTc oranlarını karşılaştırarak çocuklarda aritmi riskini belirleyebilecek öncelikli bir belirteç olup olmadığını değerlendirmektir.

Gereç ve Yöntem: Çalışmamızda Ocak 2018 ve Ağustos 2019 tarihleri arasında Eğitim ve Araştırma Hastanesi Çocuk Acil servisine QTc uzaması yapan ilaçlarla zehirlenme nedeniyle ilk 6 saat içerisinde başvuran ve çocuk acilimizde takip edilen 55 hastanın dosyası retrospektif olarak incelenmiştir. Hasta dosyalarından

yaş, cinsiyet, aldığı ilaç, müracaat süresi, klinik bulgu ve fizik muayene bulgusu,vital bulgular, yapılan tedavi ve sonuçları laboratuar bulguları ve başvuru anı ve kontrol bakılan 6. saat EKG (elektrokardiyogram) bulguları, QT, QTc, Tp-e, Tp-e/QT ve Tp-e/QTc süreleri kaydedilmiştir.

Bulgular: Çalışmaya alınan hastaların yaş ortancası 155±77,2 ay idi. Kız hasta sayısı 33(%60), erkek hasta sayısı 22 (%40) idi. Çalışmamızda hastaların başvuru anı ve 6. saatte bakılan lökosit sayısı, hemoglobin, platelet, bun, kreatinin, SGPT ve kalsiyum değerleri arasında istatistiksel olarak anlamlı farklılık saptandı ($p<0.05$). CK-MB ve troponin arasında istatistiksel olarak anlamlı farklılık yoktu ($p>0,05$).EKG'lerinde QT, QTc, QT/QTc, Tp-e/QT ve Tp-e/QTc süreleri arasında istatistiksel olarak anlamlı fark saptanmadı ($p>0,05$). Tp-e/QTc süreleri ve cinsiyet arasında istatistiksel olarak anlamlı bir farklılık mevcuttu ($p<0,05$).

Sonuç: Çocuklarda QTc uzatan ilaçlarla zehirlenmelerde aritmi riskini belirlemek için QTc süresi kullanılmaya devam etmekle birlikte Tp-e ve Tp-e/QTc sürelerinin öncelik bir belirteç olup olmadığını belirlemek için daha fazla sayıda hasta populasyonu içeren çalışmalara ihtiyaç duyulmaktadır.

Introduction

Childhood intoxications are among the most common causes of emergency admission. According to the 2014 records of the American Poison Control Center, more than two million children are admitted to pediatric emergency services due to intoxication (1,2). Clinical course after drug intoxication may vary from mild clinical symptoms to severe systemic symptoms that may be life threatening. These severe effects are more pronounced in cardio toxic drugs. The frequency of intoxication with drugs cause QTc prolongation such as antiarrhythmic and antidepressants, increases in children. After taking these medications, ECG(electrocardiogram) can show symptoms ranging from sinus tachycardia to severe ventricular arrhythmias and the result can be mortality. QTc prolongation is calculated by serial electrocardiogram scans in intoxication with drugs cause QTc prolongation (Table 1), and it is tried to reduce the risk of arrhythmia by applying sodium bicarbonate and other supportive treatments to patients who are QTc interval prolonged by age (3,4).

It is suggested that Tp-e and Tp-e / QTc ratios as a new ECG finding can be used as a predictive marker for mortality in ventricular arrhythmias, long QT syndrome, sudden cardiac death, hypertrophic cardiomyopathy, myocardial infarction in adult studies. It is also thought that the Tp-e / QT ratio may be a more accurate measurement than QT, QTc and Tp-e interval independent of heart rate (5,6,7)

Although there are very few studies in the literature regarding the Tp-e / QTc ratio in children, there are no studies in intoxications related to QTc prolonging drugs. The aim of this study is to evaluate whether there is a priority marker to determine the risk of arrhythmia in children by comparing QT, QTc, QT / QTc, Tp-e / QT, Tp-e / QTc ratios in intoxication with drugs may be fatal due to arrhythmia.

Materials and Methods

Fifty five patients who were admitted to Pediatric Emergency Department of Adana City Training and Research Hospital between January 2018 and August 2019 our study within the first 6 hours due to intoxication with QTc prolonged drugs and followed up in our pediatric emergency department were included in the study. This study was a single center, retrospective, observational case series. The study was approved by the Ethics Committee of Adana City Training and Research Hospital. The files of the patients were retrospectively analyzed by age, sex, medication, time of application, clinical and physical findings, vital signs, treatment and results at the time of admission hospital and 6th hour laboratory findings and ECG findings, QT, QTc, Tp-e, Tp-e / QT and Tp-e / QTc times were recorded. The duration of follow up of our patients was twenty four hours in the pediatric emergency departmant and was followed them clinical and by monitor and ECG.

Patients who were admitted to the study in the first 6 hours and who were followed up in a pediatric emergency department who had intoxication with QTc prolonged drugs were included. Intoxication with drugs that do not prolong QTc, late admission, patients with underlying disease, use of additional medication, and results were not included the study.

Surface 12-lead ECG was gained from the files (MAC 2000 ECG Machine, GE medical systems information technologies, Inc., WI, USA) with a sinus rhythm of 1 mv / 10 mm and 25 mm / sec standard calibration. Tp-e / QTc ratios were calculated by measuring the interval from the peak of the T wave

Table 1. QTc prolongation drugs

Antiarrhythmic drugs;
Quinidine, procainamide, disopyramide
Flecainide, pilsicainide, propafenone
Amiodarone, dronedarone, vernakalant
Sotalol
Dofetilide, ibutilide
Antianginal drugs
Ranolazine, ivabradine
Anticholinergic drugs (antimuscarinics)
Solifenacin, tolterodine
Anti-infective drugs
Antimalarial: Delamanid, quinidine, quinine Chloroquine, halofantrine, piperaquine
Antituberculous: Bedaquiline
Azole antifungals: Fluconazole, voriconazole,Itraconazole,
Clofazimine
Fluoroquinolones (systemic): Gemifloxacin, levofloxacin, moxifloxacin, sparfloxacin,ciprofloxacin, norfloxacin, ofloxacin
Foscarnet
HIV antiretrovirals: Saquinavir,Efavirenz, lopinavir-ritonavir, rilpivirine
Macrolide antibiotics: Azithromycin, erythromycin, clarithromycin,roxithromycin, telithromycin
Pentamidine
Pentavalent antimonials (antiparasitic/antiprotozoal):Meglumine antimoniate, sodium stibogluconate
Telavancin
Antihistamines
Astemizole, bilastine, hydroxyzine, terfenadine
Antineoplastic drugs
- Arsenic trioxide, ivosidenib, lenvatinib, vandetanib
- Ceritinib, crizotinib, dasatinib, encorafenib, gilteritinib, inotuzumab ozogamicin, midostaurin, nilotinib, osimertinib, ribociclib, toremifene, vemurafenib

Analgesic, anesthetic, and sedative drugs
- Anesthetic/sedative: Chloral hydrate, propofol
- Opioids: Buprenorphine, hydrocodone, loperamide ,methadone

Bronchodilators (beta-2 agonists)
- Arformoterol, albuterol, formoterol, levalbuterol, indacaterol, olodaterol, salmeterol, terbutaline, vilanterol

Diuretics
Gastrointestinal drugs
- Antidiarrheal: Loperamide
- Antiemetics: Droperidol, ondansetron (risk with IV use greater than oral)
- Granisetron, dolasetron, hydroxyzine, tropisetron
- Promotility: Cisapride, domperidone, metoclopramide
- Proton pump inhibitor

Neurologic drugs
Apomorphine, deutetrabenazine, donepezil, ezogabine, fingolimod, pimavanserin, tetrabenazine
Psychotropic drugs
Antipsychotics: Chlorpromazine, IV haloperidol, ziprasidone
Amisulpride, clozapine, flupentixol, haloperidol (oral), olanzapine, quetiapine, risperidone, thioridazine
Asenapine, iloperidone, paliperidone, pimavanserin
Tricyclic and tetracyclic antidepressants (TCAs; including doxepin)
Selective serotonin reuptake inhibitors: Citalopram, escitalopram, fluoxetine
Atomoxetine, trazodone, valbenazine
Vasodilator drugs
Bepridil, cilostazol
Other drugs and herbs
Miscellaneous: Anagrelide, alfuzosin, cocaine, eliglustat, gadobenate dimeglumine, lofexidine, mifepristone, papaverine (intracoronary), pasireotide, probucol, terlipressin
Herbs: Cinchona (contains quinine), licorice extract (glycyrrhizin) in overuse leading to electrolyte changes
Toxic exposure: Organophosphate insecticide

to the end of the T wave, measuring the QT interval from the beginning of the QRS complex to the end of the T wave and calculating QTc = QTd √ (RR interval) according to the corrected QTc Bazett formula (Figure 1) (8).

Statistical Analysis

IBM SPSS Statistics Version 20.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as mean and standard deviation (where necessary, median and minimum - maximum). The t test was used to compare categorical variables between groups.The Shapiro Wilk test was used to test whether the numerical measurements provided the normal distribution assumption. T test was used to compare numerical measurements between the groups. Statistical significance was taken as 0.05 in all tests.

Results

Fifty five patients who were admitted to our study within the first 6 hours due to intoxication with QTc prolonged drugs and followed up in our pediatric emergency department were included in the study. The median age of the patients was 155 ± 77.2 months. The number of female patients was 33 (60%) and the number of male patients was 22 (40%). Antidepressants and antipsychotics were the most commonly used drugs. All of the patients were followed-up in the pediatric emergency observation and discharged (Table 2).

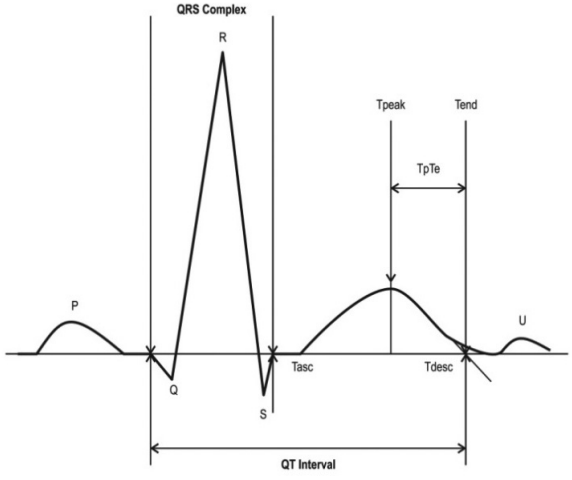

Figure 1. Measurement of QT and Tp-e interval in ECG (8).

Table 2. Epidemiological characteristics of patients

Gender	**n(%)**
Female	33(60)
Male	22(40)
Age	155±77.2 month
TIME of ARRIVAL HOSPITAL	
0-1 hour	27(49.1)
1-6 hour	28(50.9)
TYPE of DRUGS	
Antipsychotics / antidepressant	31(56.4)
-Selective seronin reuptake inhibitors	15(27.2)
-Tricyclic and tetracyclic antidepressants	5(9)
-Risperidone	6(10.9)
-Quetiapine	3(5,5)
-Olanzapine	1(1.8)
-Haloperidol	1(1.8)
Antiarrhythmic	5(9.1)
-Beta blocker	3(5.4)
-Ca channel blockers	2(3.7)
Antiepileptic	3(5.5)
-Gabapentin	2(3.7)
-Carbamazepine	1(1.8)
Antipsychotics + other	3(5.5)
-Risperidone+Metoclopromide	1(1.8)
-Tricyclic and tetracyclic antidepressants+Proton pump inbitor	2(3.7)
Antiarrhythmic + other	1(1.8)
-Beta blocker+proton pump inhibitor	1(1.8)
Antihistamine	2(3.6)
-Desloratadin	2(3.6)
Antihypertensive	1(1.8)
-Metildopa	1(1.8)
Antiepileptic + Antihypertensive	1(1.8)
-Metildopa+carbamazapine	1(1.8)
Antidepressant + Antibiotics + other	1(1.8)
-SSRI+Nidazol+phenylephrine	1(1.8)
Antidepressant + Antiepileptic	1(1.8)
-Quetiapine+valproic acid	1(1.8)
Other	6(10.9)
-Organophosphate insecticide	1(1.8)
-Metoclopromide	2(3.6)
-Proton pump inbitor	1(1.8)
-Phenylephrine+chlorpheniramine	2(3.6)

Table 2. continued

NUMBER OF DRUGS	
Single	40(72.7)
Multipl	15(27.3)
CLINIC	
No symptoms	46(83.6)
Central nervous system (CNS) symptoms	7(12.7)
Gastrointestinal system (GIS) symptoms	1(1.8)
CNS + GIS symptoms	1(1.8)
Cardiovascular system symptoms	1(1.8)
Respiratory system symptoms	0(0)
TREATMENT	
Gastric lavage, Activated Charcoal	55(100)
Hydration intravenose saline	55(100)
Observation	55(100)
Other (alkalinization)	1(1.8)
HOSPITALIZATION	
Pediatric Emergency Department	55(100)
RESULT	
Recovery	55(100)
Exitus	0(0)

There was a statistically significant difference between leukocyte count, hemoglobin, platelet, blood urea nitrogen, creatinine, SGPT and calcium values at the time of admission hospital and after 6 hours ($p<0.05$). There was no statistically significant difference between CK-MB and troponin levels ($p>0.05$). The comparison of laboratory results is summarized in Table 3.

In the ECG of the patients at the time of admission; QT interval was 0.31 ± 0.04 ms, QTc interval was 0.40 ± 0.03 ms, QT / QTc ratio was 0.78 ± 0.10 ms Tp-e / QT ratio was 0.23 ± 0.04 ms and Tp-e / QTC ratio was 0.18 ± 0.02 ms. And control ECG at the 6th hour; the QT interval was 0.32 ± 0.04 ms, the QTc interval was 0.40 ± 0.03 ms, the QT / QTc ratio was 0.79 ± 0.09 ms, the Tp-e / QT ratio was 0.22 ± 0.05 ms, and the Tp-e /QTc ratio was 0.17 ± 0.03 ms. There was no statistically significant difference between the groups ($p>0.05$) (Table 4). There was a statistically significant difference between Tp-e / QTc ratio and gender ($p<0.05$) (Table 5).

Discussion

Sudden cardiac arrest may develop after drug-induced QT prolongation. Although the arrhythmia side effects associated with QT prolonging drugs are known, cardiac side effects and ECG findings are

Table 3. Comparison of the results of the laboratory at the time of admission hospital and control

	First (n=55) (mean±SD)	6th Control (n=55) (mean±SD)	p
WBC (10^3 µL)	10.82±3.84	9.25±3.17	<0.05
Hgb (g/dL)	12.68±1.47	12.27±1.53	<0.05
Htc (%)	36.18±6.37	35.73±4.17	0.510
PLT (10^3 µL)	318.12±95.5	285.82±77	<0.05
Glucose (mg/dL)	102.61±30.54	96.61±21.31	0.280
Bun (mg/dL)	23.82±7.29	21.70±6.33	<0.05
Creatinin (mg/dL)	0.44±0.17	0.40±0.18	<0.05
SGOT (U/L)	27.5±9.23	26±9.5	0.057
SGPT (U/L)	15.2±5.57	14±4.74	<0.05
Sodium (mmol/L)	138.32±2.23	138.7±2.05	0.305
Potassium (mmol/L)	3.97±0.39	4±0.31	0.073
Calcium (mg/dL)	9.79±0.52	9.46±0.48	<0.05
CK-MB (ng/mL)	3.53±3.79	2.62±2.30	0.116
Troponin-I (ng/mL)	2.62±2.43	2.89±3.26	0.633

Table 4. Comparison of the results of electrocardiography at the time of admission hospital and control

ECG	First (mean±SD)	6th Control (mean±SD)	p
Pulse(min)	103.31±30	98.96±30	0.106
QT DII (ms)	0.31±0.04	0.32±0.04	0.416
QTc DII (ms)	0.40±0.03	0.40±0.03	0.522
QT/QTc (ms)	0,78±0.10	0.79±0.09	0.251
Tp-e/QT DII	0.23±0.04	0.22±0.05	0.118
Tp-e/QTc DII	0.18±0.02	0.17±0.03	0.375

Table 5. Comparison of electrocardiography results by gender

ECG	Female (n=33) (mean±SD)	Male (n=22) (mean±SD)	p
Admission hospital			
QT DII(ms)	0.32±0.04	0.31±0.04	0.308
QTc DII(ms)	0.40±0.02	0.31±0.04	0.193
QT/QTc(ms)	0,80±0.11	0.74±0.09	0.074
Tp-e/QT DII	0.22±0.04	0.24±0.05	0.112
Tp-e/QTc DII	0.17±0.02	0.18±0.03	0.687
Control			
QT DII(ms)	0.32±0.03	0.32±0.04	0.675
QTc DII(ms)	0.40±0.02	0.40±0.03	0.330
QT/QTc(ms)	0,79±0.09	0.80±0.09	0.826
Tp-e/QT DII	0.21±0.04	0.23±0.05	0.175
Tp-e/QTc DII	0.16±0.02	0.18±0.03	<0.05

not clear. In the literature, QT, QTc, Tp-e, QT / QTc interval, especially Tp-e / QT and Tp-e/QTc ratio, have been shown to be indicative of the total distribution of repolarization. In the use of QTc prolonging drugs, it is necessary to evaluate the QTc interval for diagnostic and follow-up by examining the ECGs of the patients, and also to utilize the Tp-e interval which can show the distribution of total repolarization of the ventricle to determine the risk of arrhythmia (9,10,11).

There are a limited number of studies on QT prolongation in children in the literature. Although the studies are related to the use of drugs in the treatment dose, there are no studies on poisoning with QT prolonging drugs. Our study was carried out in a patient group who presented with intoxication with QT prolonging drugs for accident or suicide purposes. Antipsychotic and antidepressant take was the most common intoxication agent (56.4%). Okayasu H et al. (2019) In a study evaluating arrhythmia effects of antidepressants, they found QTD and QTc interval to be high but there was no significant difference in Tp-e and Tp-e / QT ratio (12,13,14).

It has been shown in the literature that antiepileptic drugs may also cause sudden cardiac arrhythmias (15). Kwon S et al. found a normal QT and QTc interval in a study with antiepileptics. They did not find any significant difference when compared with gender (16). Lee JH et al. In their study with ondansetron and sevoflurane, the other drugs that caused QTc prolongation, they showed that sevoflurane prolonged QTc interval, QTc and Tp-e interval were prolonged in the ondansetron group but there was no change in Tp-e / QT ratio (17). In another study conducted in children, it was observed that sevoflurane used during anesthesia increased QT and QTc interval and did not change Tp-e interval (18). Similarly, Mehta D et al in their study with droperidol and ondansetron did not find a significant difference in QT and Tp-e interval (19). In our study, no statistically significant difference was found between the time of admission

and 6th hour control QT, QTc, Tp-e / QT and Tp-e / QTc ratio (p>0.05). Although the mechanism of action of the drugs varies depending on the number of patients included in the study, we think that we did not find any significant change in the duration of the study as a result of early admission to the emergency department.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recommended the use of QT / QTc ratio to clinically assess the potential for arrhythmia in non-arrhythmic drugs. They made this suggestion because QTc calculated by Bazzett formula could be interpreted as prolonged by mistake at high heart rates (20). There was no statistically significant difference between QT / QTc ratio in our study (p>0.05).

In previous studies, it has been shown that QT interval is affected by sex, while the duration of QT in adolescents is shorter in boys and girls in younger children. In the study of Banatar A et al., No difference was found between the sexes in QT interval up to 10 years, but longer QT and QTc interval in girls over 10 years (21). There is no clear data in the literature regarding Tp-e and Tp-e / QTc ratio. In our study, there was no statistically significant difference between the QT, QTc and Tp-e / QT ratio between the male and female groups (p>0.05).

Impaired electrolyte values, underlying cardiac disease, and additional drug use may also lead to QT prolongation (16). There was a statistically significant difference between leukocyte count, hemoglobin, platelet, bun, creatinine, SGPT and calcium values at the time of admission and after 6 hours (p<0.05). There was no significant difference in other laboratory values. We think that the changes in the laboratory values of the patients are due to hydration especially after the treatment.

The retrospective nature of our study and the insufficient number of cases in our study and the lack of a control group were the limitations of our study.

As a result, QTc prolonging drugs may cause sudden arrhythmia and cardiac arrest. QTc durations and arrhythmia risk continue to be determined in ECG. Prospective studies involving a large number of patient groups are needed to predict which parameters should be used to determine the risk of arrhythmia in children with these drugs.

Ethics

Ethics Committee Approval: The study received an approval from the Adana City Training and Research Hospital.

Authorship Contributions

Availability of data and materials: All materials taken from other sources (including our own published writing) were clearly cited. S.S.G. contributed to study concept and design. S.S.G. and B.T. contributed to analysis and interpretation of the data. S.S.G. and B.T. contributed to drafting of the manuscript. All authors read and approved the final version of the manuscript.

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