

Drug-induced Torsades de Pointes in patients aged 80 years or more

Seksen yaş ve üstü hastalarda ilaçlara bağlı Torsades de Pointes

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ABSTRACT

Objective: We studied all English-written peer-reviewed reports on drug-induced Torsades de Pointes (TdP) in patients aged 80 years or more in order to characterize the clinical circumstances leading to this serious complication.

Methods: Our literature search yielded 24 reports on 25 patients aged 80-95 years with drug-induced TdP. We systematically reviewed each report and recorded the non-modifiable risk factors for drug-induced TdP (i.e., female sex and structural heart disease) as well as preventable clinical circumstances, which might have been associated with drug-induced TdP.

Results: The most prevalent risk factors for drug-induced TdP were non-modifiable risk factors: 22 (88%) patients were female patients and 19 (76%) patients had structural heart disease. Overall, 16 (64%) patients were female patients with structural heart disease. The literature did not report any elderly male patients without structural heart disease. Among the preventable clinical circumstances, which might have been associated with drug-induced TdP, the most prevalent were: administering QT prolonging agents despite long QT interval (n=11; 44%) and co-administration of two or more QT prolonging agents (n=9; 36%). The most prevalent QT prolonging agents found to trigger TdP were macrolides and quinolones (n=9; 36%). All but three patients had at least one or more preventable clinical circumstances, which might have been associated with drug-induced TdP.

Conclusion: Physicians should be more aware of the risk for drug-induced TdP in patients aged 80 years or more while administering QT prolonging agents despite long QT interval and co-administering two or more QT prolonging agents, specifically in elderly female patients with structural heart disease. (*Anadolu Kardiyol Derg 2008; 8: 260-5*)

Key words: Nonagenarians, octogenarians, Torsades de Pointes, risk factors

ÖZET

Amaç: Biz, 80 yaş ve üstü olan hastalarda ciddi komplikasyonlara yol açan ilaçlara bağlı gelişen Torsades de Pointes'in (TdP) klinik koşullarını tanımlamak için, hakemlik dergilerde İngilizce yayınlanan tüm çalışmalarını inceledik.

Yöntemler: Literatür taramamız, 80-95 yaşlarında TdP'li 25 vakayı bildiren 24 raporun sonucunu verdi. Her rapor sistematik olarak incelenip ilaca bağlı gelişen TdP için değiştirilemeyen risk faktörleri (kadın cinsiyeti ve yapısal kalp hastalığı) ve TdP'le ilişkili modifiye edilebilen klinik koşulları kaydedildi.

Bulgular: İlaçlara bağlı TdP için en yaygın risk faktörleri, modifiye edilmeyenler idi; kadın cinsiyeti (%88- 22 hasta) ve yapısal kalp hastalığı (%76, 19 hasta). Toplamda, (%64) 16 kadın hastanın yapısal kalp hastalığı var idi. Literatürde, yapısal kalp hastalığı olmaksızın herhangi bir yaşlı erkek hasta bildirilmedi.

İlaça bağlı TdP ile ilişkilendirilmiş, önlenemez klinik koşulların arasında, en yaygın arasında: Uzun QT aralığına rağmen (n= 11; %44) QT aralığını uzatan ilaçların kullanılması ve iki veya daha çok QT aralığını uzatan ilaçların kullanılması (n= 9; %36) yer almıştır. En yaygın olarak TdP'yi tetikleyen QT aralığını uzatan ilaçlar, makrolidler ve kinolonlar olduğu (n= 9; 36%) saptandı. Üç hasta dışında tüm hastalarda, ilaçlara bağlı TdP için bir veya daha fazla önlenemez klinik koşulları vardı.

Sonuç: Doktorlar, QT aralığını uzatan ilaçları 80 yaş ve üstü hastalarda, özellikle uzun QT aralığı olan ve yapısal kalp hastalıkları olan kadın hastalarda kullanırken, ilaçlara bağlı gelişen TdP'nin riskleri göz önünde tutmalıdır. (*Anadolu Kardiyol Derg 2008; 8: 260-5*)

Anahtar kelimeler: Doksan ile 99 yaşları arasındaki hastalar, 80 ile 89 yaşları arasındaki hastalar, Torsades de Pointes

Introduction

Torsades de Pointes (TdP) is a polymorphic ventricular tachycardia that may lead to ventricular fibrillation and sudden death. This potentially fatal arrhythmia is rarely associated with

congenital long-QT syndrome and mostly associated with drug administration and electrolyte imbalances. Several antiarrhythmic, anti-infective, anti-psychotic and other agents, might trigger TdP by blocking specific potassium channels in the myocyte membrane. Their effect reduces the outward potassium current

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called I_{Kr}. Inhibition of this major re-polarizing potassium current participates in prolongation of the action potential in the ventricular myocardium, and this leads to the clinical finding of QT interval prolongation and rarely to TdP (1).

Some patients might exhibit extensive prolongation of the QT interval while taking the above-mentioned drugs. Hence, they might be at risk for drug-induced TdP. Risk factors for drug-induced TdP include: female sex, hypokalemia, recent conversion from atrial fibrillation, congestive heart failure, baseline QT prolongation, severe hypomagnesaemia, and others (1, 2). Many of these risk factors are common in elderly patients. For example, congestive heart failure affects about 10% of patients aged 75 years or more (3). Additionally, the use of diuretics is prevalent in elderly patients. Diuretics might increase the risk for drug-induced TdP by causing hypokalemia and hypomagnesaemia (4, 5). Worldwide, the majority of elderly population is women. Women, elderly in particular, are at an increased risk for drug-induced TdP (1, 6). Moreover, elderly patients might have high offending drug concentrations due to decreased renal clearance, decreased hepatic metabolism, and polypharmacy-associated hepatic drug interactions (7).

Conventionally, "elderly" has been defined as a chronological age of 65 years or more (8). However, approximately one-third of elderly individuals maintain healthy lives late into their 80's and 90's (9). Since this population is expected to grow in the future, it is of great importance to study the clinical circumstances, which might lead to drug-induced TdP in octogenarians and nonagenarians. There are no reviews or clinical studies concerning drug-induced TdP or drug-induced QT prolongation in patients aged 80 years or more.

The aim of the present study is to characterize the clinical circumstances leading to drug-induced TdP in patients aged 80 years or more by systematic analysis of reports published in peer-reviewed journals.

Methods

Retrieval of case reports

This was a systematic review. We performed a literature search for all peer-reviewed reports in English on elderly patients aged 80 years or more who were diagnosed as having drug-induced TdP, until May 2008, by using the following keywords in the PubMed: "Torsades de Pointes", "Torsade de Pointes", "QT", "Arrhythmia", "Syncope", and "Sudden death". The references in each report were further reviewed for additional publications, as were relevant letters to the editor.

Exclusion of case reports

The following reports were excluded: reports on TdP not triggered by drugs; reports on drug-induced TdP in patients aged 79 years or less; reports on sudden death without documented TdP; reports published in non-peer-reviewed journals; reports on suicide attempts with very high doses of QT prolonging agents; reports on polymorphic ventricular tachycardia due to ischemia; and reports on series of patients without a detailed description of every patient.

Non-modifiable risk factors for Torsades de Pointes

Each case report was analyzed for the documented presence of non-modifiable risk factors for drug-induced TdP, i.e., female sex (6) and structural heart disease, including high-degree atrial-ventricular block (i.e., complete atrial-ventricular block, second degree Mobitz II atrial-ventricular block), bifascicular block, congestive heart failure, ischemic heart disease, left ventricular hypertrophy, and valvulopathy (1, 2). History of atrial fibrillation without mention of echocardiographic findings was not consistent with the definition of structural heart disease, although it might be associated with atrial dilatation (10).

Preventable clinical circumstances leading to Torsades de Pointes

Each case report was analyzed for the presence of preventable clinical circumstances, which might have been associated with drug-induced TdP other than the administration of a QT prolonging agent itself. For example: hypokalemia during the administration of a QT prolonging agent (see Table 1 for the complete list). QT prolonging agents were those accepted by the QTdrugs.org Advisory Board to carry a risk of TdP (11). Hypokalemia was defined as potassium serum levels < 3.5 mmol/L (5). Hypocalcemia was defined as calcium serum levels < 8.5 mg/dL (12). Severe hypomagnesaemia was defined as magnesium serum levels < 1 mg/dL (1). Inappropriate or no adjustment of a QT prolonging agent's dosing in patients with reduced creatinine clearance or reduced hepatic metabolism was defined according to the pharmacokinetics of the offending agent. Digitalis toxicity was defined as digitalis serum levels > 2.6 ng/mL (13). Prolonged QT interval in the baseline electrocardiogram before drug initiation (4, 14), was defined as corrected QT interval (QTc) > 450 msec for both men and women and was calculated by using the Bazett's formula (15).

Statistical analysis

Descriptive statistical analysis was performed with SPSS (SPSS Inc., Chicago, IL, USA) system for Windows, version 13.0. Continuous variables, such as age and corrected QT interval, were summarized by means, standard deviation, medians and ranges.

Results

Our literature search yielded 24 reports on 25 elderly patients with drug-induced TdP (16-39). Clinical characteristics of reported patients are illustrated in Table 1. Baseline corrected QT interval was reported in 15 patients and their mean corrected QT interval was 449±33 msec (median: 450 msec; range: 387-525 msec). Baseline QT interval was reported in three patients (350 msec, 400 msec and 440 msec). Corrected QT interval following the arrhythmia was reported in 13 patients and their mean corrected QT interval was 576±83 msec (median: 544 msec; range: 480-720 msec). QT interval following the arrhythmia was reported in 6 patients and their mean QT interval was 531±97 msec (median: 560 msec; range: 360-640 msec). All patients survived the potentially fatal arrhythmia.

Incidence of non-modifiable risk factors for Torsade de Pointes

Overall, 22 (88%) patients were females and 19 (76%) patients had structural heart disease (Table 1). Reported were 16 (64%) female patients with structural heart disease, 6 (24%) female patients with no structural heart disease, and 3 (12%) male patients with structural heart disease. Elderly male patients with no structural heart disease were not reported (Table 1). On average, 1.64±0.49 non-modifiable risk factors for TdP were observed.

Preventable clinical circumstances leading to Torsades de Pointes

Among the preventable clinical circumstances, which might have been associated with drug-induced TdP, the most prevalent were: administrating QT prolonging agents despite long baseline QT interval or long corrected QT interval (n=11; 44%), co-administration of two or more QT prolonging agents (n=9; 36%), not adjusting QT prolonging agents' doses to the decreased creatinine clearance (n=5; 20%), and hypokalemia during the administration of QT prolonging agents (n=4; 16%). All

but three patients were reported to have one preventable clinical circumstance, which might have been associated with drug-induced TdP. Fifteen (60%) patients were reported to have two or more preventable clinical circumstances, which might have been associated with drug-induced TdP (Table 2). On average, 1.8±1.1 preventable clinical circumstances associated with drug-induced TdP were observed.

Overall risk factors and clinical circumstances leading to Torsades de Pointes

All the patients had two or more non-modifiable risk factors for TdP and/or preventable clinical circumstances, which might have been associated with drug-induced TdP. Moreover, 15 (60%) patients had four or more non-modifiable risk factors for TdP and/or preventable clinical circumstances, which might have been associated with drug-induced TdP (Fig. 1).

Drugs that triggered Torsades de Pointes

The most prevalent drugs to trigger TdP were macrolides and quinolones (n=9; 36%). The rest of the drugs to trigger TdP were anti arrhythmic agents (n=6), psychotropic agents (n=4), anti-histamines (n=3) and terodiline (n=3) (Table 3).

Table 1. Clinical characteristics of reported patients

Age, year	Mean±SDs	84.0±3.8
Hx of cardiomyopathy/LVH	n (%)	4 (16)
Hx of ischemic heart disease	n (%)	5 (20)
Hx of congestive heart failure	n (%)	9 (36)
Hx of high degree atrial-ventricular block	n (%)	6 (24)
Hx of Prior TdP/ ventricular tachycardia	n (%)	2 (8)
CHF- congestive heart failure, Hx- history; LVH left ventricular hypertrophy; TdP- Torsades de Pointes		

Discussion

In most nations around the world, the 80-year-old and over age group is rapidly growing. By 2050, this age group is projected to number almost 379 million worldwide – 5.5 times as many as in 2000 (40). As this age group continues to grow, so does its susceptibility to drug-induced TdP, because female gender, congestive heart disease, diuretics therapy, decreased renal clearance, and decreased hepatic metabolism are all prevalent in these ages (1-7). Since physicians are going to face more of these high-risk patients in the future, it is of great importance to

Table 2. Preventable clinical circumstances, which might have been associated with drug-induced TdP and the non-modifiable risk factors for drug-induced TdP among the 25 reported patients

References	Preventable clinical circumstances which might have been associated with drug-induced TdP	Number of patients, n (%)
16, 18, 22, 23, 26, 30, 32, 33, 36, 38, 39	Administrating QT prolonging agents despite baseline long QT interval	11 (44)
16, 17, 18, 20, 21, 23, 25, 27, 33	Co-administration of two or more QT prolonging agents	9 (36)
16, 19, 20, 31, 35	QT prolonging agents' dose not adjusted to creatinine clearance	5 (20)
16, 21, 31, 34	Hypokalemia during QT prolonging agents' administration	4 (16)
26, 27, 33	Administrating QT prolonging agents despite history of TdP	3 (12)
22, 28, 38	Administrating QT prolonging agents during acute myocardial infarction	3 (12)
18, 19	Administrating QT prolonging agents during atrial fibrillation conversion	2 (8)
18, 28	Continuing QT prolonging agents despite QT prolongation	2 (8)
30	QT prolonging agents' dose not adjusted to reduced hepatic metabolism	1 (4)
25	Administrating QT prolonging agents although syncope has not been investigated	1 (4)
31	Digitalis toxicity during the administration of QT prolonging agents	1 (4)
Non-modifiable risk factors for drug-induced TdP		
All, except for 20, 23, 25	Female gender	22 (88)
All, except for 19, 21, 26, 27, 30, 39	Structural heart disease	19 (76)
TdP - Torsades de Pointes		

study the clinical circumstances, which might lead to drug-induced TdP in octogenarian and older patients.

We sought to study patients aged 80 years or more who had drug-induced TdP while being prescribed with QT prolonging agents. Physicians who prescribe QT prolonging agents should consider drug interactions, hepatic metabolism, renal clearance, electrolyte disturbances, and QT prolongation before and during the treatment. In other words, we aimed to study if the physicians who prescribed the QT prolonging agents had been judicious enough with their prescriptions and took all the necessary safety measures. We found that all but three patients had at least one preventable clinical circumstance, which might have been associated with drug-induced TdP other than the administration of a QT prolonging agent itself. Moreover, 60% of the patients had two or more preventable clinical circumstances which might have been associated with TdP. Administering QT prolonging agents despite baseline long QT interval, and co-administration of two or more QT prolonging agents, were the two most prevalent preventable clinical circumstances which might have been associated with drug-induced TdP. Hence, we believe that the physicians who had prescribed the QT prolonging agents were not judicious enough in its use.

Overall, 88% of all patients were female patients, 76% of all patients had structural heart disease, and 64% of all patients were female patients with structural heart disease. This observation is consistent with previous reports: female patients have a longer QT interval than male patients (41), they have more pronounced QT prolongation when challenged with potassium channel blockers (42), and they are at a higher risk for developing drug-induced TdP when treated with antiarrhythmic drugs or during spontaneous bradyarrhythmias (6). Patients with heart failure have down regulation of potassium channels leading to

action potential prolongation (43). Also, left ventricular dilatation is associated with down-regulation of the gap-junction protein connexin43 (44). All these factors significantly increase the duration and the dispersion of repolarization to predispose a given patient to TdP when challenged with a drug that further impairs repolarization. For these reasons, it is well established that elderly female patients and patients with structural heart disease are at increased risk for drug-induced TdP (1).

Administering QT prolonging agents despite long baseline QT interval was the most prevalent preventable clinical circumstance, which might have been associated with drug-induced TdP. Moreover, in two reports, QT prolonging agents were continued despite an increasing QT interval. This is not surprising; according to Viskin et al., less than 50% of cardiologists and less than 40% of other physicians can accurately calculate a corrected QT interval, and less than 25% of cardiologists and other physicians can identify a long QT when they see one. Moreover, in the presence of a U wave, many physicians have a difficulty deciding where the T wave ends and the U wave begins (45). It is also difficult to distinguish between a U wave and a biphasic T wave (46). The absence of down-stroke in the T waves also makes it difficult to measure the QT interval. Due to the diverse spectrum of medications that might trigger TdP (1), and because patients aged 75 years or more take an average of six different medications (47), physicians in all fields of medicine and in geriatrics in particular, should be able to recognize a long QT when they see one. With that emphasized, efforts should be made at all levels of medical education to increase the awareness of prolonged QT interval.

Co-administration of two or more QT prolonging agents, which was present in 36% of the patients, has long been recognized as an important risk factor for drug-induced TdP (1). According to Curtis et al., 22% of outpatients with overlapping prescriptions for two or more QT prolonging agents are elderly (48). Unfortunately, some physicians ignore the "black-box" warning labels made by the pharmaceutical companies, which are attached to these agents. For example, terfenadine was withdrawn from the American market in 1998 following unsuccessful attempts to limit its administration together with other arrhythmogenic agents (49). Since the number of drugs associated with adverse interactions continuously increases, and since polypharmacy is common in the elderly (47), it is not practical to remember all the potential adverse interactions without the aid of computer-generated warnings at the time of drug prescription or drug dispense. In the meanwhile, physicians can find updated information regarding the risk for QT prolongation for a given drug and the risk for drug interactions in the Internet (50).

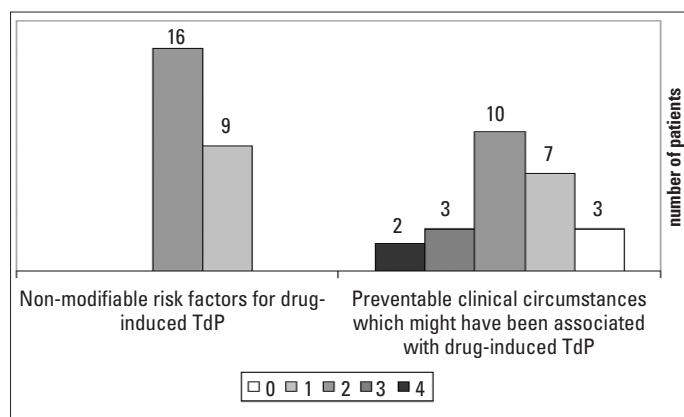


Figure 1. Number of patients with Torsades de Pointes (TdP) by number of risk factors for TdP

Table 3. Drugs that triggered Torsades de Pointes

Antibiotic agents	Anti-arrhythmics	Psychotropic agents	Anti-histamines
Erythromycin (n=4)	Sotalol (n=3)	Amitryptiline (n=1)	Astemisol (n=2)
Roxithromycin (n=2)	Ibutilide (n=1)	Haloperidol (n=1)	Terfanidine (n=1)
Gatifloxacin (n=2)	Quinidine (n=1)	Fluoxetine (n=1)	
Clarithromycin (n=1)	Amiodarone (n=1)	Risperidone (n=1)	
Levofloxacin (n=1)			

Limitations of the study

Our study was based on published case reports. We assume that there are many more incidents of drug-induced TdP in patients aged 80 years or more that have not been published; when a similar incidence involving a given agent has already appeared in print several times; when a report is rejected from publication because TdP is attributed to early multiple risk factors for TdP rather than to initiating the offending drug; or when physicians are reluctant to report their deceased patients. Indeed, in all the cases we studied, the patients survived the arrhythmia. Patients with sudden death without documentation of an arrhythmia would also go unrecorded. We believe that our results are, therefore, more likely an underestimation of the true prevalence of clinical circumstances, which might lead to drug-induced TdP in octogenarians and older patients. On the other hand, a control group of younger patients or patients who did not develop TdP was not studied. Hence, we cannot estimate the incidence of TdP in patients aged 80 years or more, or if our findings are implacable to other age groups as well.

Clinical implications

According to our findings, the majority of patients aged 80 years or more with drug-induced TdP developed the arrhythmia despite an easily identified clinical circumstance, which might have been associated with drug-induced TdP. We believe that previous recommendations regarding taking measures before prescribing any QT prolonging agent are particularly relevant to patients aged 80 years or more: elderly female patients with structural heart disease should be treated more cautiously (1). Obtaining a baseline electrocardiogram (ECG) and another ECG following the first doses of QT prolonging agents are advisable, particularly when prescribing two or more QT prolonging agents, although the efficacy and cost-effectiveness of doing so have not been established. If the corrected QT interval exceeds 450 msec, physicians should avoid prescribing QT prolonging agents or should decrease the QT prolonging agent's dose. It is also advisable to monitor the potassium serum levels frequently, especially in patients treated with diuretics.

Conclusions

Physicians who prescribe QT prolonging agents should consider drug interactions, hepatic metabolism, renal clearance, electrolyte disturbances, and QT prolongation before and during the treatment, especially in patients aged 80 years or more.

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