Epidemiology of symptomatic drug-induced long QT syndrome and torsade de pointes in Germany

Giselle Sarganas¹, Edeltraut Garbe¹,²,³, Andreas Klimpel¹, Rolf C. Hering¹, Elisabeth Bronder¹, and Wilhelm Haverkamp⁴*

¹Clinical Pharmacology and Toxicology, Charite´ Universita¨tsmedizin Berlin, Chariteplatz 1, 10117 Berlin, Germany; ²Department of Clinical Epidemiology, BIPS – Institute for Epidemiology and Prevention Research, Achterstr. 30, 28359 Bremen, Germany; ³Faculty of Human and Health Sciences, University of Bremen; and ⁴Department of Cardiology, Campus Virchow Clinic, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

Received 26 March 2013; accepted after revision 9 June 2013; online publish-ahead-of-print 5 July 2013

Aims
Drug-induced long QT syndrome (diLQTS) leading to Torsade de Pointes (TdP) is a potentially lethal condition, which has led to several post-marketing drug withdrawals in the past decade. The true incidence of diLQTS/TdP is largely unknown. One explanation is under-reporting of this potentially life-threatening adverse event by physicians and other medical staff to pharmacovigilance agencies. To gain more insight into the incidence of diLQTS and TdP, the Berlin Pharmacovigilance Center (PVZ-FAKOS) has actively and prospectively identified patients who developed this particular type of drug-induced adverse event. Here, the basic characteristics of the affected patients are summarized and suspected drugs are discussed. Furthermore, an extrapolation of the Berlin incidence rates to the German Standard Population is presented.

Methods and results
Using a Berlin-wide network of 51 collaborating hospitals (>180 clinical departments), adult patients presenting with long QT syndrome (LQTS/TdP) between 2008 and 2011 were identified by active surveillance of these hospitals. Drug exposures as well as other possible risk factors were obtained from the patient’s files and in a face-to-face interview with the patient. One-hundred and seventy patients of possible LQTS/TdP were reported to the Pharmacovigilance Center of whom 58 cases were confirmed in a thorough validation process. The majority (66%) of these cases were female and 60% had developed LQTS/TdP in the outpatient setting. Thirty-five (60%) of 58 confirmed cases were assessed as drug-related based on a standardized causality assessment applying the criteria of the World Health Organization. Drugs assessed as related in more than two cases were metoclopramide, amiodarone, melperone, citalopram, and levomethadone. The age-standardized incidence of diLQTS/TdP in Berlin was estimated to be 2.5 per million per year for males and 4.0 per million per year for females.

Conclusion
While European annual reporting rates based on spontaneous reports suggest an annual diLQTS/TdP incidence of 0.26 per million in Germany, we estimated a considerably higher incidence of diLQTS/TdP in an active surveillance approach. Further measures are warranted to better sensitize physicians against this potentially life-threatening drug-induced adverse event.

Keywords
Drug-induced long-QT syndrome • Torsade de Pointes • Incidence • QT/QTc prolongation • Pharmacoepidemiology • Germany

Introduction
Abnormal QT/QTc prolongation can lead to a polymorphic ventricular tachyarrhythmia, termed Torsade de Pointes (TdP), which was first described in 1966 by the French cardiologist Francois Dessertenne.¹ Torsade de Pointes typically causes syncope, but may also lead to sudden cardiac death (SCD). There are two forms of abnormal QT/QTc prolongation, the congenital and the acquired variant. The latter is most often associated with drugs prolonging the QT/QTc interval. Drug-induced long QT syndrome (diLQTS) has been the most common cause of withdrawal of marketed drugs in the last two decades.²–⁴ It has been demonstrated that most of the drugs...
associated with diLQTS/TdP block a particular cardiac potassium current, i.e. the delayed rectifier potassium current. This current is crucial for regulation of normal myocardial repolarization.5,6

Data from the World Health Organization (WHO) Uppsala Monitoring Centre have shown that most spontaneous diLQTS/TdP reports are related to classes I and III antiarrhythmics (e.g. class I: quinidine; class III: amiodarone, sotalol) followed by antimicrobial drugs (e.g. macrolides).7 It has been estimated that the incidence of diLQTS/TdP associated with quinidine, a class I antiarrhythmic, is between 2.0 and 8.8%8–10 and with di-sotalol, a beta-blocker with additional class III antiarrhythmic properties, between 1.8 and 4.8%.11–13 The incidence of diLQTS/TdP under non-cardiac drugs is considerably lower, for instance, for moxifloxacin it is estimated to be ~4 per 7.7 million patients.14 A study from the US Food and Drug Administration (FDA) Adverse Event Reporting System using data from 2004 to 2008 found a total of 374 reports of diLQTS/TdP to be associated with antimicrobial drugs, of which 62% were related to antibacterials and within this group mostly to macrolides and fluoroquinolones.15 Antipsychotic (e.g. haloperidol and thioridazine) and antidepressant drugs (e.g. amitriptyline) may also induce abnormal prolongation of the QT/QTc interval, making the treatment of patients with major mental illness often difficult.16 Numerous published case reports and case series of affected patients suggest that diLQTS/TdP is far from being a problem that may be neglected. According to pharmacovigilance data, the annual reporting rates of diLQTS/TdP per million population vary between 1.2 in Sweden, 0.26 in Germany, and 0.08 in Italy.17 Owing to the unknown real incidence and the under-reporting rate of diLQTS/TdP, the Berlin Pharmacovigilance Center (PVZ-FAKOS) has prospectively identified patients with LQTS/TdP to conduct a case–control surveillance study (FAKOS). Here, we summarize the basic characteristics of the affected patients and discuss the suspected drugs. Furthermore, the incidences rates for Berlin are calculated and extrapolated to the German Standard Population.

Methods

FAKOS was initiated in 2000 as a pharmacovigilance project to study serious rare toxicity of drugs within the adult (≥18 years old) source population of Berlin (2.89 million inhabitants). The study has been described in more detail elsewhere.18–20 Between 1 March 2008 and 31 December 2011, LQTS/TdP was one of the target diseases of FAKOS. In an active surveillance approach, LQTS/TdP patients were identified in 51 collaborating hospitals including >180 clinical departments of all disciplines of Internal Medicine including Cardiology, Psychiatry, Neurology, Anaesthesiology, and Emergency Room Care. The concept of the study was presented in the hospitals and the physicians received the study materials including a checklist for LQTS/TdP with inclusion and exclusion criteria to allow a rough screening among their patients for recruitment. For that screening, physicians were using an automatic QTc measurement. More than 250 physicians collaborated as contact partners for FAKOS. To actively identify cases, FAKOS contacted these physicians every 2–4 weeks by fax, e-mail, or telephone.

Case definition

Patients had to have an age of ≥18 years and electrocardiographic evidence of a heart rate corrected QT prolongation of ≥450 ms for men and ≥470 ms for women (a normal QRS interval duration provided), and at least one of the following clinical signs/symptoms: (i) electrocardiographic evidence of TdP (at least three consecutive QRS complexes with alternating axis); (ii) successful cardiac resuscitation; (iii) syncope; or (iv) severe dizziness. The QT interval was corrected for the heart rate by using Bazett’s formula (\( QTc = QT/\sqrt{RR} \)). Patients with complete bundle-branch block (BBB), an implanted cardiac pacemaker, or an implanted cardioverter-defibrillator were excluded.

Case identification and validation

After notifying a patient with LQTS/TdP to the study centre, an initial telephone call with the treating physician was conducted to check the inclusion and exclusion criteria. In case of patient eligibility, a trained staff member of FAKOS obtained the patient’s informed consent and conducted a standardized personal interview in the hospital, ascertaining all relevant information. The results of all relevant laboratory tests and other investigations including copies of all available 12-lead electrocardiograms (ECGs), and other diagnostic and therapeutic information were documented by the treating physician and served subsequently for case validation. All ECGs were manually re-measured by an experienced ECG reader. A detailed review of the case by a cardiology expert was required for case validation.

Drug intake and standardized drug causality assessment in individual cases

Previous (4 weeks before index date) and current drug intake was ascertained in a face-to-face patient interview and from the medical charts. A possible drug aetiology was assessed for each case in a standardized causality assessment according to the criteria of the WHO assessment method which includes the categories ‘certain’, ‘probable’, ‘possible’, ‘unlikely’, ‘unclassified’, and ‘unclassifiable’.21 A drug reaction was evaluated as ‘certain’, when the time relationship to drug intake was plausible, other causes could be ruled out, a clinically reasonable reason on drug withdrawal (‘positive dechallenge’) was observed, and LQTS/TdP was observed on re-exposure to the same drug (‘positive rechallenge’). The causality assessment was ‘probable’, when LQTS/TdP occurred with a reasonable time sequence to administration of the drug, it was unlikely to be attributed to other causes, and a positive dechallenge was observed on drug withdrawal. The drug reaction was ‘possible’, when there was a plausible time sequence to drug intake; however, another cause could not be ruled out and information on dechallenge was lacking, unclear, or negative. For all drugs involved, an extensive literature search from published reports was performed, which aimed to retrieve all available information regarding the effect of the individual drugs on myocardial repolarization, i.e. the QT/QTc interval. Suspected drugs were grouped according to the
Anatomical Therapeutic Chemical (ATC) Classification System and analysed by descriptive statistics.

**Estimation of the incidence of drug-induced long QT syndrome/Torsade de Pointes**

For estimation of the annual incidence rate of diLQTS/TdP in Berlin, all validated diLQTS/TdP cases within the study period from March 2008 to December 2011 were considered. The average crude annual incidence rate of diLQTS/TdP per million population was calculated by the number of these events divided by the person-time at risk during the study period (3.83 years) multiplied by one million. For this calculation, the size of the adult population in Berlin was taken with 2.89 million inhabitants as has been published in 2010. The denominator thus included 11.10 million person-years at risk (2.89 million inhabitants × 3.83 study years). The crude annual Berlin incidence rate was standardized by age and sex with the direct method using the German Standard Population for the year 2010 as reference population.

FAKOS was supported by a grant from the Federal Institute for Drugs and Medical Devices (BfArM) in Germany. The study was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin, informed consent was obtained from all patients who participated in the study.

**Results**

Between March 2008 and December 2011, 170 possible cases were reported to the study centre. After an initial check of the inclusion and exclusion criteria through a telephone call with the treating physician, 48 patients had to be excluded because they were under the age of 18 years; the QTc prolongation was below the threshold for inclusion; they had an asymptomatic episode, a complete BBB, an implanted cardiac pacemaker, or an implanted cardioverter-defibrillator. From the remaining 122 patients, 8 were not able to conduct the interview because of poor health state, bad mental health, or because they had already been discharged from the hospital; 8 patients had died and 8 patients declined to participate. With the remaining 98 cases, interviews were conducted and relevant clinical and drug information was collected and ECGs were ascertained. After the validation process including manual re-measurement of the ECGs by an experienced reader, 40 out of these 98 cases were not included. The reasons were: the re-measured QTc was normal (n = 12), the re-measured QTc interval was prolonged, but without confirmed symptoms (n = 27), and existence of right BBB (n = 1) (Figure 1). Basic characteristics of all

![Flowchart of LQTS case validation FAKOS.](https://academic.oup.com/europace/article-abstract/16/1/101/464241/11101464441)
58 validated cases who fulfilled the above mentioned inclusion and exclusion criteria are presented in Table 1. The majority (66%) were female and the mean age was 56.7 ± 19.7 years. Thirty-five cases (60%) had developed their index event in the outpatient setting, while 23 (40%) had developed it while staying in a hospital. The majority of the cases (n = 35, 60%) were treated in a cardiology department.

The presence of known risk factors for LQTS/TdP was found in 57% (n = 33) of the cases, 43% (n = 25) underwent cardiac reanimation, 48% (n = 28) presented with syncope, and 40% (n = 23) with severe dizziness. Forty-two patients (72%) presented with severe QTc prolongation and were defined as a QTc ≥ 500 ms (maximum 741 ms).

The mean age of diLQTS/TdP cases was 61.1 ± 18.7 years old. The majority (63%) were female cases. Among these cases, 22 (63%) presented with TdP, 16 (46%) underwent cardiac reanimation, 14 (40%) presented with syncope, and 14 (40%) with severe dizziness. The potassium level at the event date was available in 20 out of 35 cases. The majority of these cases (60%) had hypokalaemia at the event date ranging from 2.11 to 3.40 mmol/L (Table 1).

A total of 42 different drugs were assessed as at least possibly related to LQTS/TdP, and some of these drugs were assessed as related several times (Table 2). The number of possibly related drugs varied between 1 and 4 per case. For 12 cases, only one drug was assessed as related, for a further 12 cases two drugs, for 9 cases three drugs, and for 2 cases four drugs, respectively. The most frequently suspect drug groups were psycholeptics/psychoanalptics (ATC N05, N06), drugs from the cardiovascular system (ATC C01), and anti-infectives (ATC J01) (Table 2). Drugs assessed as related in more than two cases were metoclopramide, amiodarone, melperone, citalopram, and levomethadone. The calculated annual crude incidence rate of diLQTS/TdP in Berlin was 3.2 per million person-years. Table 3 shows the age- and sex-standardized incidence rates of diLQTS/TdP for adults (≥18 years of age) in Berlin and Germany. Adult males in Berlin had a diLQTS/TdP incidence rate of 2.5 per million person-years, while it was 4.0 per million person-years for adult females.

**Table 1** Basic characteristics of all validated LQTS/TdP cases and diLQTS/TdP cases

<table>
<thead>
<tr>
<th></th>
<th>All validated LQTS/TdP</th>
<th>Only diLQTS/TdP</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n = 58 (100%)</td>
<td>n = 35 (100%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>56.7 ± 19.7</td>
<td>61.1 ± 18.7</td>
</tr>
<tr>
<td>Clinical sign/symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsade de Pointes</td>
<td>33 (57%)</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>Cardiac reanimation</td>
<td>25 (43%)</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>28 (48%)</td>
<td>14 (40%)</td>
</tr>
<tr>
<td>Severe dizziness</td>
<td>23 (40%)</td>
<td>14 (40%)</td>
</tr>
<tr>
<td>Severe QTc (&gt;500 ms)</td>
<td>Range 501–741 ms</td>
<td>Range 501–741 ms</td>
</tr>
<tr>
<td></td>
<td>42 (72%)</td>
<td>25 (71%)</td>
</tr>
<tr>
<td>Risk factors and co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>20 out of 38 measured (53%)</td>
<td>12 out of 20 measured (60%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (12%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (9%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>9 (16%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>11 (19%)</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>25 (26%)</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>Acute ischaemic heart disease</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

**Discussion**

We have presented the age- and sex-standardized incidence rate of diLQTS/TdP in Berlin and suspected drugs involved. While based on the pharmacovigilance spontaneous reporting system, the annual reporting rate of diLQTS/TdP in Germany was 0.26 per million person-years, whereas, according to our active surveillance study, the crude incidence of diLQTS/TdP was considerably higher (3.2 per million person-years).

We are only aware of one other publication which provided an estimate of the incidence of diLQTS/TdP. This retrospective study from southwest France estimated a crude incidence of 10.9 per million per year. The higher incidence in this study might be due to its less stringent inclusion criteria. For our study, the electrocardiographic evidence of prolonged QTc/TdP was a prerequisite, while the French study also recruited cases based on diagnoses in medical records/text information without requiring electrocardiographic evidence of QTc/TdP. Besides this, the source population of the French study might actually be slightly higher than it was considered in the calculation of the incidence rate due to possible referrals from rural areas to city hospitals in which the cases were identified. The fact that until now there is no designated specific code for LQTS/TdP in the International Classification of Diseases 10th revision (ICD-10) makes it difficult to estimate its incidence retrospectively. In the ICD-10 coding system, LQTS/TdP cases tend to be masked under the codes I47.2 [ventricular tachycardia (VT)], I49.0 [ventricular fibrillation (VF)], or I46.1 SCD.
It has been estimated that among all cases diagnosed with VT, VF, or SCD, between 5 and 7% were LQTS/TdP cases.\textsuperscript{17}

In our prospective active surveillance study, case validation included two steps. In the first step, eligibility of the patient was broadly checked by asking the inclusion and exclusion criteria to the treating physician. In the second step, a thorough validation of the whole case including ECG reading by an experienced cardiologist was conducted. In this second step, 40 out of 98 cases were not included. Among these 40 cases, the reason for not including 12 cases was that they had a normal QTc interval pointing to the importance of manual ECG reading for making this diagnosis. Some physicians tended to confuse QT with QTc when reporting the case. This fact of failing to identify a prolonged QT interval has been previously reported.\textsuperscript{25,26} Physicians should thus be sensitized to this drug-induced side effect and the pitfalls when reading the ECG.

Our study confirmed several known risk factors for diLQTS/TdP. This was the case for female sex, which has repeatedly been reported as a risk factor of diLQTS/TdP.\textsuperscript{27–30} Even though potassium in blood was not measured in all patients, among those who were measured, the majority had hypokalaemia accompanying the diLQTS/TdP. Hypokalaemia is a well-known risk factor for diLQTS/TdP, as it decreases the repolarizing current by enhanced inactivation or

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Drug class & No. of different drugs & ATC classification & Drug name & No. of reactions (probable; possible) \\
\hline
Gastrointestinal system & 1 & A03FA01 & Metoclopramide & 4 (1; 3) \\
Cardiovascular system & 7 & C01BD01 & Amiodarone & 10 (7; 3) \\
 & & C01BD07 & Dronedarone & 1 (0; 1) \\
 & & C01BC04 & Flecainide & 1 (0; 1) \\
 & & C10AA04 & Fluvasstatin & 1 (0; 1) \\
 & & C09BA09 & Fosinopril + hydrochlorothiazide & 1 (0; 1) \\
 & & C03AA03 & Hydrochlorothiazide & 1 (0; 1) \\
 & & C07AA07 & Sotalol & 2 (2; 0) \\
Pituitary and hypothalamic hormones & 1 & H01BA04 & Terlipressin & 2 (2; 0) \\
Anti-infectives & 9 & J05AB01 & Aciclovir & 1 (0; 1) \\
 & & J01DD04 & Ceftriaxon & 1 (0; 1) \\
 & & J01MA02 & Ciprofloxacins & 1 (0; 1) \\
 & & J01FA09 & Clarithromycin & 1 (0; 1) \\
 & & J01EE01 & Cotrimoxazol & 1 (0; 1) \\
 & & J05AB06 & Ganclovir & 1 (0; 1) \\
 & & J01MA12 & Levofloxacins & 1 (1; 0) \\
 & & J01MA14 & Moxifloxacins & 2 (1; 1) \\
 & & J01CR05 & Piperacillin + Tazobactam & 1 (0; 1) \\
Antineoplastic/immunomodulants & 4 & L01BC02 & 5-Fluorouracil & 1 (0; 1) \\
 & & L01XA03 & Oxaliplatin & 1 (0; 1) \\
 & & L01XC03 & Trastuzumab & 1 (0; 1) \\
 & & L04AD02 & Tacrolimus & 2 (1; 1) \\
Muscle relaxants & 1 & M03AB01 & Suxamethonium & 1 (0; 1) \\
Analgesics & 2 & N01AH01 & Fentanyl & 1 (1; 0) \\
 & & N02AX02 & Tramadol & 1 (1; 0) \\
Antiepileptics & 2 & N03AF01 & Carbamazepin & 1 (1; 0) \\
 & & N03AG01 & Valproic acid & 1 (1; 0) \\
Psycholeptics/psychoanaleptics & 13 & N06AB04 & Citalopram & 3 (2; 3) \\
 & & N06AA12 & Dextepin & 1 (1; 0) \\
 & & N06AB10 & Escitalopram & 1 (1; 0) \\
 & & N06AB03 & Fluoxetine & 2 (2; 0) \\
 & & N05AD01 & Haloperidol & 2 (1; 1) \\
 & & N06AA02 & Imipramine & 1 (1; 0) \\
 & & N05AD03 & Melperone & 3 (2; 1) \\
 & & N06AX11 & Mirtazapine & 2 (2; 0) \\
 & & N05AH03 & Olanzapine & 2 (2; 0) \\
 & & N05AG02 & Pimozide & 1 (1; 0) \\
 & & N05CM22 & Promethazin & 1 (1; 0) \\
 & & N05AH04 & Quetiapin & 2 (1; 1) \\
 & & N05AC02 & Thoridazine & 1 (1; 0) \\
Other nervous system drugs & 2 & N07BC07 & Levomethadone & 3 (2; 1) \\
 & & N07BC02 & Methadone & 2 (2; 0) \\
Total & 42 & & & \\
\hline
\end{tabular}
\caption{Drug-induced long QT syndrome/Torsade de Pointes suspected drugs}
\end{table}
exaggerated competitive block of sodium and it potentiates drug blockade of the residual current. Even a minor reduction in the repolarizing current, for example, by hypokalaemia, may become obvious when further stressors to repolarization, such as drug challenge are superimposed. Heart failure and coronary artery disease are also considered risk factors for diLQTS/TdP. Among the six cases with heart failure and diLQTS/TdP, two also had concomitant hypokalaemia. Two patients presented with an acute coronary syndrome, which may also have contributed to the clinical manifestation of diLQTS. Hypothyroidism, which was found in four diLQTS/TdP cases, is another risk factor, as it causes bradycardia, which can physiologically prolong ventricular repolarization. Acute alcohol withdrawal has been documented to increase QT variability and thus increase repolarization liability. Among our diLQTS/TdP cases, four had alcoholism as a co-morbidity.

A substantial fraction (60%) of all validated LQTS/TdP cases was attributed to drug therapy. Of all suspected drugs, 19 out of 42 (45%) are listed in the ARIZONA CERT List, an online source which updates drugs suspected to cause LQTS/TdP on the basis of clinical evidence from the literature and drug labelling information. Amiodarone—a well-known cause of LQT3—was suggested as the causative drug in 10 cases of our study. It is of interest in this respect that the drug was administered orally in half of these patients (5 out of 10) and in the other half intravenously. Among the drugs not listed in the ARIZONA CERT List, several drugs have been identified as possible causes of LQTS/TdP in other studies: mirtazapine (two suspected cases) and fentanyl (one suspected case) were similarly identified in the study by Poluzzi and colleagues, which analysed data from the FDA Adverse Event Reporting System from 2004 to 2007. This study identified 10 reports for mirtazapine and calculated an adjusted reporting odds ratio (ROR) of 3.5 (95% CI 1.8–6.8) for the drug, whereas 11 reports were identified for fentanyl with an adjusted ROR of 1.5 (95% CI 0.8–2.7). Terlipressin, which was in two cases, a suspected drug in our study, was suggested to induce LQT/TdP in two case reports. Melperone, which was a suspected drug in three of our cases, was found to cause QT prolongation in the study of Hui et al. Olanzapine suspected in two of our cases was identified as cause of a significant prolonged QTc interval in the Rotterdam population-based cohort study.

<table>
<thead>
<tr>
<th>Age</th>
<th>Annual number of incident cases in Berlin</th>
<th>Population Berlin</th>
<th>Incidence rate per million</th>
<th>Standard population Germany</th>
<th>Expected incident cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9.1</td>
<td>2 890 391</td>
<td>(Crude rate) 3.2</td>
<td>67 436 494</td>
<td>222.2</td>
</tr>
<tr>
<td>Male</td>
<td>3.4</td>
<td>1 400 686</td>
<td>(Male crude rate) 2.4</td>
<td>32 623 751</td>
<td>81.7</td>
</tr>
<tr>
<td>Female</td>
<td>5.8</td>
<td>1 489 705</td>
<td>(Female crude rate) 3.9</td>
<td>34 812 743</td>
<td>139.8</td>
</tr>
</tbody>
</table>

Standardized incidence rate: 222.2/67 436 494 = 3.3 per million.
Standardized male incidence rate: 81.7/32 623 751 = 2.5 per million.
Standardized female incidence rate: 139.8/34 812 743 = 4.0 per million.

Table 3: Annual expected diLQTS/TdP cases and age–sex standardized diLQTS/TdP incidence per 1 million per year (directly standardized to the adult German standard population (≥18 years old))
diLQTS has prognostic implications. In that study, patients with severe drug-induced QTc prolongation (QTc > 500 ms) had a four-fold higher mortality rate during follow-up compared with patients with a QTc < 500 ms.

Study strengths and limitations

To our knowledge, this is the first study that provides an estimate of the incidence of diLQTS/TdP throughout a prospective active surveillance approach, which in our study involved all 51 Berlin hospitals covering the whole population of Berlin. The true estimate of diLQTS/TdP for Germany could still be somewhat higher than what we have found, since we were not able to validate 24 possible cases because they either declined to participate (n = 8), or were not able to conduct the interview (n = 8), or because they had died (n = 8). Furthermore, completely undetected cases are likely, if hospitals failed to notify all possible cases to the study centre. Other patients may have died, making the diagnosis diLQTS impossible.

However, this underascertainment may have been partly counterbalanced by also including cases with a ‘possible’ causal drug relationship in the estimate of diLQTS/TdP, since not in all possible cases the drug may have had a causal role. On the other hand, if we had only included cases with a ‘probable’ causal relationship, underascertainment of diLQTS/TdP would have been highly likely, since most patients were taking more than one drug and therefore would have received a causality assessment of ‘possible’. To produce a more accurate estimate, our study only considered the manual measurement of ECGs by an experienced reader as recommended by the ICH E14 guideline rather than the automated measurement, as sometimes the ECGs can yield misleading results in the presence of noise or when dealing with abnormal ECG rhythms, low-amplitude P- or T-waves, or overlapping U-waves.

Conclusion

Drug-induced long QT syndrome leading to TdP is a serious and still underestimated adverse drug reaction. Physicians prescribing drugs prolonging myocardial repolarization must be aware of the fact that drugs that prolong myocardial repolarization may induce severe, potentially life-threatening ventricular arrhythmia. Our data suggest that further measures are warranted to better sensitize physicians against this particular type of potentially life-threatening drug-induced adverse event.

Acknowledgements

The LQTS/TdP cases and controls were identified within the PVZ-FAKOS study. We thank all hospitals, clinicians, collaborators, and especially the patients who contributed to data collection.

Conflict of interest: E.G. is running a department that occasionally performs studies for pharmaceutical industries with the full freedom to publish. The companies include Mundipharma, Bayer, Stada, Sanofi-Aventis, Sanofi-Pasteur, Novartis, Celgene, and GSK. She has been consultant to Bayer-Schering, Nycomed, Teva, GSK, and Novartis in the past. The present work is unrelated to the above grants and relationships.

Funding

The PVZ-FAKOS study was supported by a grant from the Federal Institute for Drugs and Medical Devices (Bonn, Germany).

References

Multiple accessory pathways in a patient with congenitally corrected transposition of the great arteries and severe malformation of the coronary sinus

Antonio Hernández-Madrid*, Inmaculada Sánchez, and Roberto Matia

A 29-year-old patient diagnosed with (S,L,L) congenitally corrected transposition of great arteries (CCTGA) and pre-excitation is presented. We performed a coronary angiogram and it documented a coronary sinus with multiple branches and right atrium fistulas. Note the venous return shows a dual coronary venous system, with a remnant of the left superior venacava draining in the ‘left’ coronary sinus (white arrows) marking the level of the true AV groove, and a prominent ‘right’ coronary venous system at the ‘right’ AV groove fistulas (red arrow). Three accessory pathways were ablated. To our knowledge, this severe malformation of the coronary venous system has not been previously described.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/multiple-accessory-pathways.pdf