

Macrolides and Torsadogenic Risk: Emerging Issues from the FDA Pharmacovigilance Database

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Abstract

Introduction: Concern exists on the pro-arrhythmic potential of macrolides, namely *Torsade de Pointes* (TdP). Recent evidence has challenged the common opinion of considering azithromycin a safer therapeutic option, causing emerging regulatory and clinical interest.

Materials and Methods: We analyzed cases of drug-induced TdP (2004-2011) submitted to the publicly available FDA Adverse Event Reporting System (FAERS). Four groups of mutually exclusive events were identified in decreasing order of drug-attributable risk: 1) TdP; 2) QT interval abnormalities; 3) ventricular arrhythmia (VA); 4) Sudden Cardiac Death (SCD). They were combined into case definition A (TdP/QT abnormalities) and case definition B (VA/SCD). Both case-by-case analysis (information on concomitant drugs, especially QT-prolonging agents listed by Arizona CERT, and disproportionality approach (Reporting Odds Ratio, ROR, with 95%CI) were carried out.

Results: Over the 8-year period, macrolides were associated with 183 and 419 cases of interest (case definition A and B, respectively). Clarithromycin was the most frequently reported (84 and 162 cases), followed by azithromycin (63 and 140). Only 27% of cases of TdP/QT abnormalities with azithromycin occurred in patients >65 years of age (63, 47 and 44% for clari-, ery- and telithromycin, respectively). In cases of TdP/QT abnormalities, concomitant QT-prolonging drugs (Arizona CERT lists 1 or 2) were recorded with a proportion very different among macrolides (11 to 89%). The highest percentage of fatal outcome was recorded for azithromycin (17%). Disproportionality was found for azithromycin, clarithromycin and telithromycin for both events of interest, whereas erythromycin showed disproportion only for TdP/QT abnormalities.

Conclusions: Despite inherent limitations of spontaneous reporting analyses, the remarkable proportion of fatal cases and the occurrence of TdP-related events in middle-aged patients strengthen the view that caution is needed before considering azithromycin as a safer therapeutic option among macrolides.

Keywords: Spontaneous reporting systems; Disproportionality; Azithromycin

Introduction

Macrolides are a class of concern for arrhythmia, especially *Torsade de Pointes* (TdP) and its surrogates: QT interval prolongation, ventricular arrhythmia (VA), such as ventricular tachycardia, fibrillation and subsequent Sudden Cardiac Death (SCD) [1]. It is generally believed that erythromycin (in particular, intravenously) carries the highest risk, while azithromycin is thought to have only a minimal effect on the cardiovascular system [2].

However, a recent cohort study by Ray et al. [3], found increased risk of cardiovascular death during a 5-day azithromycin treatment (as compared to amoxicillin and ciprofloxacin, with a risk similar to levofloxacin). Because no formal comparison was undertaken among macrolides, the question arises whether or not we are dealing with a class effect. Notably, the FDA is reviewing this safety aspect for potential regulatory measures with related clinical implications. In addition, several drug utilization studies underlined an increased use in the population over the past decade, both in US and Europe, a scenario suggesting inappropriate prescription [4-8].

Therefore, we provide the contribution of pharmacovigilance by critically exploring the FDA Adverse Event Reporting System (FAERS). Despite inherent limitations, FAERS offers public access to raw data, covers virtually the entire population (by including US reports and serious/unexpected events from Europe) and has been recently used to investigate rare events such as TdP that may otherwise be undetected in

dedicated clinical trials [9,10]. In addition, interest is emerging in using FAERS to obtain reliable within-class comparisons [11,12].

Materials and Methods

Case definition

Taking into account the multifaceted clinical presentation of TdP, a multidisciplinary panel of experts (i.e., cardiology, pharmaco-epidemiology and pharmacovigilance) reached consensus on definition of drug-induced TdP, by identifying 4 groups of events reflecting a decreasing order of drug-attributable risk: 1) TdP; 2) QT interval abnormalities (including QT prolongation and shortening); 3) ventricular arrhythmia (VA, including ventricular fibrillation/tachycardia); 4) Sudden Cardiac Death (SCD). These groups were mutually exclusive (i.e. a single case report of arrhythmias was classified

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Received January 26, 2013; **Accepted** February 11, 2013; **Published** February 13, 2013

Citation: Raschi E, Poluzzi E, Koci A, Moretti U, Sturkenboom M, et al. (2013) Macrolides and Torsadogenic Risk: Emerging Issues from the FDA Pharmacovigilance Database. J Pharmacovigilance 1: 104. doi:10.4172/2329-6887.1000104

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only in one group with the following priority: 1>2>3>4). In this study, these four groups were combined as follows: TdT with QT abnormalities (case definition A), VA with SCD (case definition B).

Before performing the analysis, several technical issues were handled with. This is the case for the drug mapping, duplicate removal and management of missing data [13]. Data of interest for the 2004-2011 period were collected from “DEMO” (demographic information), “DRUG”, “REACTION” (adverse events coded according to the Medical Dictionary for Regulatory Activities terminology, MedDRA version 13.0) and “OUTCOME” files [14].

Data analysis

In the light of the peculiar clinical setting in which TdP usually occurs (i.e., multi-factorial causative roles with different risk factors), a case listing was first generated in order to describe demographic information (e.g., age and sex) and concomitant drugs, which may act as potential confounders of the drug-event association by reducing the so-called “repolarization reserve” [15]. Specifically, each event of interest was assessed for co-administration of drugs with cardiovascular indications (i.e., Class III antiarrhythmic drugs, *proxy* of already diagnosed arrhythmia; digitalis, diuretics, beta blockers, calcium channel blockers and ACE inhibitors/ARBs, *proxies* of heart disease) and agents with TdP liability listed by the AZCERT website (as of November 9th, 2012). In addition, the seriousness of the event was retrieved by checking information on the outcome (i.e., whether or not the event was fatal).

Moreover, disproportionality analysis was performed by calculating the Reporting Odds Ratio (ROR), with corresponding 95% Confidential Interval (CI). Statistical significance was formally defined when the lower limit of the 95% Confidence Interval (95%CI) was >1, with at least 3 cases. We gained insight into the temporal appearance of disproportionality for azithromycin and TdP/QT abnormalities by providing a cumulative time-series analysis of the ROR [16].

Only reports where macrolides were recorded as suspect (e.g., “primary” or “secondary” suspect) or interacting drug were considered. In addition, reports with missing information on age and gender were excluded. The statistical package SPSS (version 19.0) was used.

Results

Over the 8-year period, 2,679,762 spontaneous reports were retrieved after removal of duplicates and multiple records. Overall, a total of 7,844 (6,056 with at least one active substance) and 72,366 (55,854 with at least one active substance) cases were retrieved (case definition A and B, respectively). Macrolides, lincosamides and streptogramins (J01F) were reported in 197 and 480 events of interest (A and B, respectively).

Table 1 shows the complete case listing (i.e., demographic data, information on concomitant drugs and is proportionality analysis). Macrolides were associated with 183 and 419 cases of interest (TdP/QT abnormalities and VA/SCD, respectively). Clarithromycin was the most frequently reported drug (84 and 162 cases), followed by azithromycin (63 and 140).

Most of the cases occurred in females. In addition, only 27% of cases of TdP/QT abnormalities with azithromycin occurred in patients of >65 years of age, whereas this percentage was much higher for clari-, ery- and telithromycin: 63, 47 and 44, respectively.

Remarkably, QT-prolonging drugs of the Arizona CERT lists 1 or 2 were concomitantly recorded in 59% of cases of TdP/QT abnormalities associated with azithromycin (45, 89 and 11%, with clari-, ery- and telithromycin, respectively). Concomitant drugs with cardiovascular indication were reported in 22% of cases with azithromycin (21, 10 and 5%, with the other macrolides). Fatal outcome was found in 17% of azithromycin cases and in 4, 11 and 11% with clari-, ery- and telithromycin, respectively.

A disproportionality signal was found for azithromycin, clarithromycin and telithromycin for both events of interest. Erythromycin showed disproportion only for TdP/QT abnormalities; the 31 cases of VA/SCD did not provided statistically significant ROR.

The time-trend analysis showed a steady number of TdP/QT abnormality reporting in the last 4 years; disproportionality was already significant in 2007-Q2 (ROR=2.15; 95% CI=1.07-4.32; Figure 1) and ROR values increased up to 5.02 (95% CI=3.47-7.26) in 2010-Q1.

Discussion

All the widely used macrolides, including azithromycin, are

Table 1: Data mining of the FAERS database (2004-2011 period). Only macrolides with at least one case of interest are shown.

Macrolide (AZCERT List)	N. cases (% F)	Age (0-17; 18-65; >65)	By MD	N. cases with c.v. drugs#	N. cases with AZCERT drugs (List 1; 2; 3) #	N. Fatal cases	ROR (95%CI)
TdP+QT Abnormalities							
Azithromycin (I)	63 (67)	3; 43; 17	30	14	23; 11; 3	11	5.69 (4.43-7.31)*
Clarithromycin (I)	84 (55)	3; 28; 53	33	18	37; 18; 1	3	6.23 (5.01-7.74)*
Erythromycin (I)	19 (68)	2; 8; 9	6	2	8; 3; 6	2	5.28 (3.35-8.32)*
Telithromycin (II)	18 (78)	0; 10; 8	7	1	0; 1; 1	2	3.35 (2.11-5.34)*
Roxithromycin (II)	1 (0)	0; 1; 0	1	0	0; 1; 0	0	n.a.
Spiramycin (n.r.)	1 (100)	0; 0; 1	0	1	0; 0; 0	0	n.a.
VA+SCD							
Azithromycin (I)	140 (54)	16; 94; 30	66	6	13; 24; 14	54	1.35 (1.14-1.60)*
Clarithromycin (I)	162 (54)	6; 86; 70	48	11	15; 35; 12	63	1.28 (1.09-1.49)*
Erythromycin (I)	31 (48)	6; 14; 11	10	3	3; 9; 0	15	0.91 (0.64-1.31)
Telithromycin (II)	89 (61)	0; 60; 29	52	3	8; 7; 4	27	1.83 (1.48-2.27)*
Roxithromycin (II)	7 (43)	0; 2; 5	3	0	1; 2; 0	2	1.72 (0.80-3.68)

n.a.: not applicable due to the low number of cases (see methods).

where at least one cardiovascular or AZCERT drug is reported among suspect, interacting or concomitant drugs.

AZCERT List I: Drugs with risk of TdP; List II: Drugs with possible risk of TdP; n.r.: not reported.

* statistically significant ROR (i.e.. 95%CI>1). MD: Medical Doctor

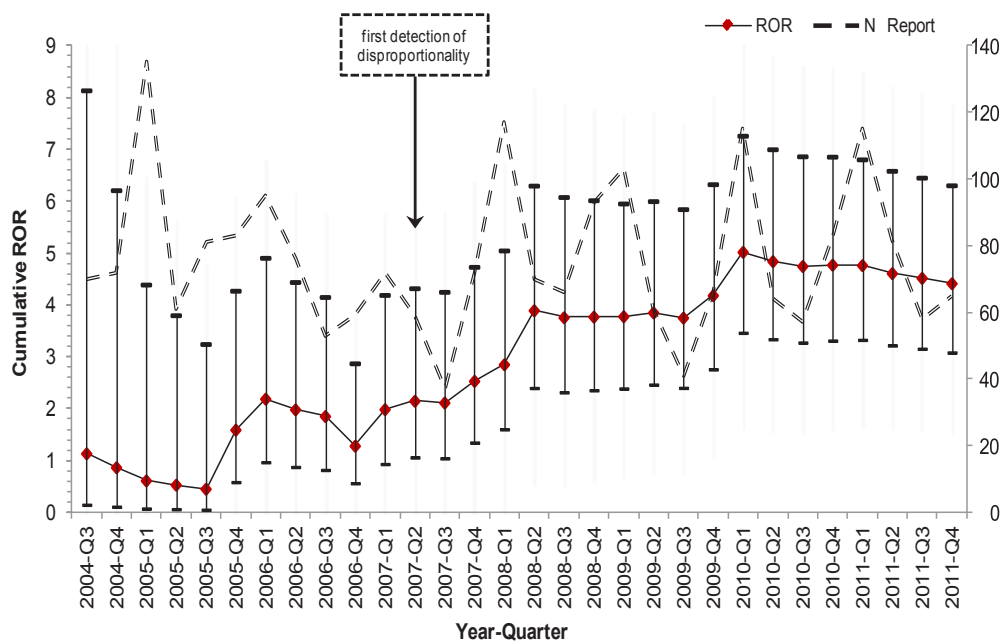


Figure 1: Time trends of cumulative ROR with corresponding 95%CI for TdP and QT abnormalities associated with azithromycin (full line), and relevant total number of spontaneous reports (dotted line). Arrow with box indicates the first appearance of a statistically significant disproportionality (2007-Q2).

associated with disproportionality for TdP-related events, suggesting potential signals of torsadogenicity. This is in line with literature data and information from the Arizona CERT, which considers azithromycin, clarithromycin and erythromycin as having a risk of TdP [17,10].

Based on our data, we believe that including azithromycin in AZCERT list 1 appears prudent, especially in the light of recent emphasis on its novel unlicensed clinical roles (e.g., chronic obstructive pulmonary disease, cystic and non-cystic fibrosis) [18-20]. Our analysis found a remarkable fraction of cases resulting in a fatal outcome, especially for azithromycin, in line with the study by Ray et al. [3]. These finding should be carefully considered, also in the light of a recent observational study showing that azithromycin is the most common prescribed drug (after amiodarone) within 48 hours prior to admission to cardiac unit for QT prolongation and mainly continued during hospitalization [21].

Considering azithromycin a safer option among macrolides in healthy patients appears unjustified, as suggested by the large number of cases occurring in middle-aged patients, who theoretically carry a reduced host-related risk. In addition, the vast proportion of cases with concomitant QT-prolonging drugs (i.e., listed by the Arizona CERT lists 1 and 2) underline the high potential of drug interaction when macrolides are co-administered with other agents undertaking a hepatic metabolism. As a matter of fact, dual intertwined mechanisms (pharmaco-kinetic and -dynamic) are responsible for macrolide-associated TdP: metabolic liability (i.e., the inhibitory effect on CYP3A4) and intrinsic hERG-blocking property [1,2]. Actually, azithromycin showed lower interaction with CYP3A4 as compared to other macrolides whether or not this theoretical advantage represents an effective clinical benefit requires clinical confirmation [22]. In patients with un-modifiable risk factors for TdP occurrence, prescribers should consider alternatives to macrolides.

The clinical implications of our results should be viewed with caution, especially in the light of well-known bias affecting pharmacovigilance data (e.g., quality and completeness of reports, external factors influencing the pattern of reporting, under-reporting and lack of exposure data). Therefore, incidence cannot be determined [23,24]. In addition, concomitant reporting of other drugs with known QT liability is only an indicator of potential drug interaction. Other types of information are needed to assess whether or not the interaction actually occurs (e.g., temporal plausibility, which only rarely is recorded in FAERS). Moreover, the supposed safer cardiac profile of azithromycin could have caused the channeling bias of preferring azithromycin in patients at risk of TdP.

Nevertheless, this pharmacovigilance analysis depicts the current situation, which is not influenced by the introduction of novel macrolides and/or antibiotics, recent regulatory measures and, therefore, probably reflects the actual scenario. Our findings corroborate the notion that concomitant drugs with QT liability may significantly impact the occurrence of arrhythmia. Thus, it is imperative that clinicians not only submit adverse event reports to the FDA, but provide complete and accurate information to adequately inform the causality assessment. As previously shown, most patients experiencing TdP had more than two risk factors before the initiation of antibiotic therapy [25]. Therefore, our results strengthen the importance of accurately evaluating medical history (especially concomitant drug administration) to identify patients susceptible to arrhythmia.

In conclusion, our study suggests that in clinical practice azithromycin carries a level of risk similar to other macrolides: the notable proportion of fatal cases and the occurrence of TdP-related events in middle-aged patients strengthen the view that caution is needed before considering azithromycin as a safer therapeutic option among macrolides. Appropriate prescription of all macrolides is therefore vital and should be based on the underlying disease, patient's risk factors, concomitant drugs and local pattern of drug resistance.

Acknowledgements

The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2013) under grant agreement n° 241679 – the ARITMO project.

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