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Antimicrobials and the Risk of Torsades de Pointes

The Contribution from Data Mining of the US FDA Adverse Event Reporting System

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Abstract

Background: Drug-induced torsades de pointes (TdP) is a complex regulatory and clinical problem due to the rarity of this sometimes fatal adverse event. In this context, the US FDA Adverse Event Reporting System (AERS) is an important source of information, which can be applied to the analysis of TdP liability of marketed drugs.

Objective: To critically evaluate the risk of antimicrobial-induced TdP by detecting alert signals in the AERS, on the basis of both quantitative and qualitative analyses.

Methods: Reports of TdP from January 2004 through December 2008 were retrieved from the public version of the AERS. The absolute number of cases and reporting odds ratio as a measure of disproportionality were evaluated for each antimicrobial drug (quantitative approach). A list of drugs with suspected TdP liability (provided by the Arizona Centre of Education and Research on Therapeutics [CERT]) was used as a reference to define signals. In a further analysis, to refine signal detection, we identified TdP cases without co-medications listed by Arizona CERT (qualitative approach).

Results: Over the 5-year period, 374 reports of TdP were retrieved: 28 antibacterials, 8 antifungals, 1 antileprosy and 26 antivirals were involved. Antimicrobials more frequently reported were levofloxacin (55) and moxifloxacin (37) among the antibacterials, fluconazole (47) and voriconazole (17) among the antifungals, and lamivudine (8) and nelfinavir (6) among the antivirals. A significant disproportionality was observed for 17 compounds, including several macrolides, fluoroquinolones, linezolid, triazole antifungals, caspofungin, indinavir and nelfinavir. With the qualitative approach, we identified the following additional drugs or fixed dose combinations, characterized by at least two TdP cases without co-medications listed by Arizona CERT: ceftriaxone, piperacillin/tazobactam, cotrimoxazole, metronidazole, ribavirin, lamivudine and lopinavir/ritonavir.

Discussion: Disproportionality for macrolides, fluoroquinolones and most of the azole antifungals should be viewed as 'expected' according to Arizona CERT list. By contrast, signals were generated by linezolid, caspofungin, posaconazole, indinavir and nelfinavir. Drugs detected only by the qualitative approach should be further investigated by increasing the sensitivity of the method, e.g. by searching also for the TdP surrogate marker, prolongation of the QT interval.

Conclusions: The freely available version of the FDA AERS database represents an important source to detect signals of TdP. In particular, our analysis generated five signals among antimicrobials for which further investigations and active surveillance are warranted. These signals should be considered in evaluating the benefit-risk profile of these drugs.

Background

Drug-induced torsades de pointes (TdP) is a matter of concern for regulatory agencies and drug companies, and in the last decade was responsible for several regulatory interventions, such as withdrawal of the drug or restriction of its use. For instance, among antibacterials, grepafloxacin was withdrawn from the market in 1999[1] and many new drugs have been marketed with important warnings on this risk (e.g. telithromycin, moxifloxacin).[2]

Although several compounds within the same therapeutic class share a certain proarrhythmic potential, TdP occurrence cannot usually be considered as a class effect because it depends on the peculiarity of the molecular structure of each chemical entity.[3] Since, at present, a widely accepted method for risk classification among drugs belonging to the same therapeutic class is lacking, the choice of therapy by physicians is problematic, especially for drugs used frequently in general practice such as antimicrobials. Among these, many fluoroquinolones, macrolides and antifungals are known to be associated with cardiac arrhythmias, particularly ventricular arrhythmias, mainly TdP or QT interval prolongation, which may progress to TdP.[3,4]

From the clinical and regulatory standpoint, QT interval prolongation has been proposed as a surrogate marker of cardiotoxicity since it represents the forerunner for the occurrence of TdP.[5-10] Albeit frequently self-limiting, in about 20% of cases TdP converts into ventricular fibrillation, often resulting in sudden death. Although fatal events are rare, even a low risk is not justified for drugs with uncertain benefits, providing only symptomatic improvement of a mild disease or when safer alternatives are available.

Many efforts have been directed towards the identification of the best strategy to assess the risk of drug-induced TdP (the so-called TdP liability). The evaluation of this risk is currently based on a large set of tests, both pre-clinical and clinical, performed before the marketing authorization of each new medicine and, if needed, also for drugs already on the market.[5-10] Estimates for incidence of TdP induced by non-antiarrhythmic drugs range from 1 to 2 events per 100 000 patient-months of exposure.[11]

In pharmacovigilance, a signal has been defined by WHO as a ''reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously''.[12] Particularly for rare reactions, the postmarketing spontaneous reporting system represents the mainstay to generate alert signals that may not be detected in clinical trials.[13]

A recent article published in *Drug Safety* encouraged the use of the US FDA Adverse Event Reporting System (AERS) database for pharmacovigilance purposes, such as the generation of hypotheses to be tested in subsequent

studies and comparison of disproportionality scores under stringent criteria.[14] In addition, a previous pilot study from our group showed the feasibility of the analysis of this database to detect signals of drug-induced TdP.[15] However, at present, a systematic investigation on a therapeutic class as a whole has not been performed, especially for drugs covering a large population cluster such as antimicrobial agents.

The aim of the present study was to critically evaluate the risk of TdP induced by antimicrobial agents by detecting alert signals in the FDA AERS, using both quantitative and qualitative analyses.

Methods

The AERS is a computerized information database designed to support the FDA's postmarketing safety surveillance programme for all approved drug and therapeutic biological products. Healthcare professionals, manufacturers and consumers send reports voluntarily through the MedWatch programme.[16] AERS also includes serious and unlabelled spontaneous reports from non-US sources. These reports become part of a database, organized in compliance with the international safety reporting guidance issued by the International Conference on Harmonisation about contents and format. FDA staff code all reported adverse events using a standardized international terminology, Medical Dictionary for Regulatory Activities (MedDRA®) and uses reports from AERS in conducting postmarketing drug surveillance and compliance activities, and in responding to outside requests for information.

Since 2004, raw data extracted from the AERS database can be freely downloaded from the FDA website. Reports from January 2004 through December 2008 were downloaded from this website (http://www.fda.gov/cder/aers/extract.htm). For each quarter, tables including drug/biologic information for as many medications as were reported for the event (DRUG file) and adverse events coded by MedDRA terms (REACTION file) were considered. A unique number for identifying an AERS report allows all the information from the different files to be linked.

The Anatomical Therapeutic Chemical (ATC) code J was used to identify antimicrobials for systemic use.[17] In order to collect AERS reports containing anti-infective drugs, a drug name archive, including all generic and trade names of drugs marketed in the US and in most European countries, was created by using public lists freely available on authoritative websites.[18,19] By linking this archive with the AERS database, all records, including antimicrobials as the 'primary suspect drug', 'secondary suspect drug' or 'interaction' in the DRUG files were selected and the relevant reactions from the REACTION files were identified. From DEMO files (i.e. those including demographical data), information on 'event date', patient 'age' and 'gender', 'reporter's country' and 'reporter's type of occupation' were also retrieved. An automated multi-step process was applied to detect and exclude as many duplicates as possible in the database. This process was performed using a record-linkage strategy, which groups records overlapping in four key fields: event date, age, sex of patient and reporter's country. Records with three overlaps and just one missing datum were considered as duplicates.

In order to identify potential alert signals of TdP associated with antimicrobials, a case/non-case analysis was performed. Cases were represented by TdP reports, whereas non-cases were all reports of adverse events other than TdP. The absolute number of cases and reporting odds ratio (ROR) with a 95% confidence interval (CI) were evaluated for each drug. The ROR represents a measure of disproportionality, frequently used in spontaneous report analysis, that allows the identification of a potential association between the reporting of a drug and an adverse event.[20,21] The ROR compares the ratio of cases/non-cases of a particular drug with the corresponding ratio for all other drugs included in the entire database.[22-25] A significant disproportionality was formally defined when the lower limit of the 95% CI was >1. For this purpose, the statistical package Epi Info™, version 3.4.3 (2007), was used.[26]

Antiarrhythmic drugs are markers of an underlying cardiac disease (i.e. arrhythmia) that may act as a risk factor for the occurrence of

TdP.[3,27,28] The presence of any antiarrhythmic agent (i.e. amiodarone, azimilide, disopyramide, dofetilide, flecainide, ibutilide, mexiletine, propafenone, propranolol, quinidine and sotalol) among concomitant drugs was considered a proxy of pre-existing arrhythmia and was used to calculate the adjusted ROR.

In order to interpret potential signals in light of the best available information on TdP risk, we considered the drug lists provided by Arizona Centre of Education and Research on Therapeutics (CERT).[29] This source organizes and updates three lists of drugs to be avoided in patients with risk factors for TdP occurrence on the basis of clinical evidence from the literature and labelling information. We identified as signals those drugs associated with disproportionality, but not mentioned by Arizona CERT.

TdP is considered a 'designated medical event' (DME, i.e. a low-probability event with high drug-attributable risk);[30] thus, even a few TdP cases without known risk factors (only two to three cases) could represent a signal even if a significant disproportion is lacking (classical pharmacovigilance approach). In a further analysis, to refine signal detection, we identified TdP cases without co-medications listed by Arizona CERT. We recognized the intrinsic limitation of this (qualitative) approach because the FDA AERS database does not take into consideration other well known risk factors for TdP (e.g. congenital long QT syndrome, electrolyte imbalance, etc.), thus preventing the full application of the classical pharmacovigilance approach.

Results

Descriptive Analysis

We downloaded 1 743 234 reports from the public version of the FDA AERS database covering a 5-year period, and recognized 80% of reported drugs by using our drug name archive. After performing the de-duplication procedure, approximately 990 000 reports remained. We then analysed 2 344 112 drug-reaction pairs and retrieved 374 reports of TdP (see table I): 230 cases for 28 antibacterials, 85 cases for 8 antifungals, 58 cases for 26 antivirals and 1 case for the antileprosy drug, clofazimine.

The antibacterials most frequently reported were levofloxacin (55), moxifloxacin (37), ciprofloxacin (35), clarithromycin (22) and azithromycin (16). Among antifungals and antivirals, fluconazole (47), voriconazole (17), lamivudine (8), itraconazole (8) and nelfinavir (6) accounted for the highest number of cases.

The annual number of TdP reports for antimicrobials was about 75 on average, with a high variability among the years of reporting (e.g. 61 in 2005 and 98 in 2008). The reporting rate of TdP decreased progressively from 5.4 per 1000 total reports in 2004 to 3.2 per 1000 in 2008 because of a marked increase in the total number of reports. Females represented 60% of TdP cases (2% were missing data) and 55% of patients were at least 50 years of age (14% missing data).

Signal Detection

Among antibacterials, the most represented classes were macrolides (four molecules) and fluoroquinolones (five molecules), most of which had a statistically significant ROR. All macrolides showed a significant disproportionality: erythromycin (adjusted ROR 7.24 [95% CI 3.15, 15.94]), clarithromycin (5.76 [3.66, 8.92]), azithromycin (4.76 [2.81, 7.98]) and telithromycin (2.73 [1.10, 6.28]).

Among fluoroquinolones, significant disproportionality was obtained for moxifloxacin (adjusted ROR 9.03 [95% CI 6.43, 12.72]), levofloxacin (7.58 [5.70, 9.95]), ciprofloxacin (6.49 [4.51, 9.09]) and gatifloxacin (5.72 [2.29, 13.30]). In addition, there were TdP reports for ofloxacin, but these failed to reach the threshold for disporportionality.

Among other antibacterial classes, 16 further drugs were reported in TdP cases: disproportionality was found for linezolid (7 cases; adjusted ROR 2.80 [95% CI 1.23, 6.13]), whereas at least two cases without significant association between drug and TdP were observed for demeclocycline (2 cases, none without co-medications listed by Arizona CERT), sulfamethoxazole/trimethoprim (7 cases [2 without listed co-medications]), ceftriaxone (5 cases [3 without listed co-medications]),

Table I. Anti-infective agents associated with cases of torsades de pointes (TdP) by drug class

Antimicrobial agent	Cases	Non-cases	Crude ROR (95% CI)	Adjusted ROR (95% CI)	Cases without concomitant QT interval-prolonging drugs[a]	Listing in Arizona CERT[b]
Antibacterials for systemic use						
Tetracyclines						
demeclocycline[c]	2	15	NA	NA		NR
doxycycline	1	1015	0.61 (0.03, 3.94)	0.72 (0.04, 4.70)		NR
minocycline	1	600	1.03 (NA)	1.26 (0.07, 8.26)	1	NR
β-Lactam antibacterials						
ampicillin	1	254	2.42 (NA)	2.40 (0.12, 16.01)	1	NR
amoxicillin	3	2588	0.71 (NA)	0.78 (0.20, 2.50)		NR
piperacillin/tazobactam	4	1332	1.85 (0.59, 5.09)	2.16 (0.69, 5.99)	2	NR
cefazolin	1	812	0.76 (NA)	0.82 (0.04, 5.38)		NR
ceftriaxone	5	2182	1.41 (0.52, 3.50)	1.31 (0.48, 3.28)	3	NR
Carbapenems						
meropenem	3	657	2.81 (0.72, 8.99)	2.90 (0.73, 9.24)		NR
Sulfonamides and trimethoprim						
sulfamethoxazole/trimethoprim	7	3525	1.22 (0.53, 2.64)	1.42 (0.62, 3.08)	2	C
Macrolides						
erythromycin	7	653	6.60 (2.88, 14.34)	7.24 (3.15, 15.94)	2	A
clarithromycin	22	2531	5.37 (3.44, 8.31)	5.76 (3.66, 8.92)	10	A
azithromycin	16	2406	4.10 (2.42, 6.84)	4.76 (2.81, 7.98)	11	B
telithromycin	6	1632	2.26 (0.92, 5.21)	2.73 (1.10, 6.28)	5	B
Aminoglycoside antibacterials						
gentamicin	1	763	0.81 (NA)	0.75 (0.04, 4.89)	1	NR
amikacin	1	430	1.43 (NA)	1.33 (0.07, 8.54)		NR
Fluoroquinolones						
ofloxacin	1	765	0.80 (NA)	0.67 (0.03, 4.38)		B
ciprofloxacin	35	3554	6.10 (4.30, 8.62)	6.49 (4.51, 9.09)	20	C
sparfloxacin[c]	1	11	NA	NA		A
levofloxacin	55	4990	6.86 (5.20, 9.04)	7.58 (5.70, 9.95)	42	B
moxifloxacin	37	2912	7.88 (5.61, 11.03)	9.03 (6.43, 12.72)	29	B
gatifloxacin	6	638	5.79 (2.34, 13.36)	5.72 (2.29, 13.30)	4	B

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Table I. Contd

Antimicrobial agent	Cases	Non-cases	Crude ROR (95% CI)	Adjusted ROR (95% CI)	Cases without concomitant QT interval-prolonging drugs[a]	Listing in Arizona CERT[b]
Glycopeptide antibacterials						
vancomycin	2	2459	0.50 (0.09, 2.02)	0.48 (0.08, 1.94)		NR
teicoplanin	1	328	1.88 (NA)	1.61 (0.08, 10.64)		NR
Other antibacterials						
metronidazole	2	1864	0.66 (0.11, 2.66)	0.64 (0.11, 2.59)	2	NR
nitrofurantoin	1	626	0.98 (NA)	1.01 (0.05, 6.62)	1	NR
daptomycin	1	716	0.86 (NA)	0.82 (0.04, 5.35)	1	NR
linezolid	7	1572	2.74 (1.20, 5.94))	2.80 (1.23, 6.13)	5	NR
Antimycotics and antimycobacterials for systemic use						
Antibiotics						
amphotericin B	3	1097	1.68 (0.43, 5.37)	2.02 (0.52, 6.48)		NR
Imidazole derivatives						
ketoconazole	2	200	6.15 (NA)	7.46 (1.29, 30.98)		C
Triazole derivatives						
fluconazole	47	2229	13.12 (9.70, 17.69)	14.23 (10.54, 19.43)	30	C
itraconazole	8	973	5.07 (2.35, 10.46)	6.11 (2.82, 12.67)	3	C
voriconazole	17	1393	7.54 (4.52, 12.39)	8.52 (5.03, 13.94)	6	B
posaconazole	3	250	7.39 (1.89, 23.75)	8.43 (2.17, 27.89)		NR
Other antimycotics						
flucytosine[c]	1	51	NA	NA		NR
caspofungin	4	667	3.69 (1.18, 10.19)	3.80 (1.22, 10.69)	1	NR
Antimycobacterials						
clofazimine[c]	1	35	NA	NA		NR
Antivirals for systemic use						
Nucleosides and nucleotides						
aciclovir	1	2253	0.27 (0.01, 1.77)	0.35 (0.02, 2.28)	1	NR
ribavirin	2	7025	0.17 (0.03, 0.70)	0.21 (0.04, 0.84)	2	NR
ganciclovir	1	430	1.43 (NA)	1.94 (0.10, 12.62)	1	NR
valaciclovir	1	2903	0.21 (0.01, 1.38)	0.26 (0.01, 1.59)	1	NR
foscarnet	1	162	3.80 (NA)	5.14 (0.27, 33.70)		B

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Table I. Contd

Antimicrobial agent	Cases	Non-cases	Crude ROR (95% CI)	Adjusted ROR (95% CI)	Cases without concomitant QT interval-prolonging drugs[a]	Listing in Arizona CERT[b]
Protease inhibitors						
indinavir	3	436	4.23 (1.09, 13.57)	5.31 (1.37, 17.15)	1	NR
ritonavir	5	2573	1.20 (0.44, 2.97)	1.52 (0.56, 3.79)		NR
nelfinavir	6	784	4.71 (1.91, 10.87)	4.52 (2.38, 13.63)	2	NR
atazanavir	4	1610	1.53 (0.49, 4.21)	1.87 (0.60, 5.16)		B
darunavir	1	438	1.40 (NA)	1.90 (0.10, 13.39)		NR
Reverse transcriptase inhibitors						
zidovudine	4	1663	1.48 (0.47, 4.08)	1.99 (0.64, 5.49)	1	NR
didanosine	1	1463	0.42 (0.02, 2.73)	0.55 (0.03, 3.59)		NR
stavudine	3	1588	1.16 (0.30, 3.71)	1.51 (0.39, 4.82)	1	NR
lamivudine	8	3064	1.61 (0.75, 3.31)	2.06 (0.95, 4.23)	2	NR
abacavir	3	1223	1.51 (0.39, 4.82)	1.88 (0.48, 6.03)	1	NR
tenofovir	2	1850	0.66 (0.12, 2.68)	0.86 (0.15, 3.48)		NR
adefovir	1	445	1.32 (NA)	1.62 (0.08, 10.61)	1	NR
emtricitabine	1	447	1.38 (NA)	1.81 (0.09, 11.85)		NR
entecavir	1	441	1.39 (NA)	1.75 (0.09, 11.45)	1	NR
nevirapine	1	1669	0.37 (0.02, 2.39)	0.49 (0.03, 3.18)		NR
efavirenz	1	1997	0.31 (0.02, 2.00)	0.41 (0.02, 2.66)		NR
Neuraminidase inhibitors						
oseltamivir	1	1800	0.33 (0.02, 2.13)	0.42 (0.02, 2.73)	1	NR
Combinations for the treatment of HIV						
zidovudine/lamivudine	1	1516	0.41 (0.02, 2.64)	0.54 (0.03, 3.54)	1	NR
tenofovir/emtricitabine	1	1289	0.48 (0.02, 3.10)	0.63 (0.03, 4.13)		NR
zidovudine/lamivudine/abacavir	1	384	1.60 (NA)	2.17 (0.11, 14.14)	1	NR
lopinavir/ritonavir	3	2401	0.77 (0.20, 2.45)	1.02 (0.26, 3.24)	2	NR

a Drugs with suspected TdP liability according to Arizona CERT (www.azcert.org).[29]

b A = drugs with a risk of TdP; B = drugs with a possible risk of TdP; C = drugs with a conditional risk of TdP; NR = drugs not listed.

c These drugs have been reported in only one TdP case but were not discussed because the low number of non-cases (<60) does not guarantee interpretable results. However, they were included in the table for the sake of completeness.

CERT = Centre of Education and Research on Therapeutics; **NA** = Not Applicable; **ROR** = reporting odds ratio.

piperacillin/tazobactam (4 cases [2 without listed co-medications]), amoxicillin (3 cases [none without listed co-medications]), meropenem (3 cases [none without listed co-medications]), vancomycin (2 cases [none without listed co-medications]) and metronidazole (2 cases [both without listed co-medications]). The remaining antibacterials were reported in only one or two TdP cases.

Concerning antifungals, all triazole derivatives and caspofungin resulted in a significant ROR: fluconazole (adjusted ROR 14.23 [95% CI 10.54, 19.43]), voriconazole (8.52 [5.03, 13.94]), posaconazole (8.43 [2.17, 27.89]), ketoconazole (7.46 [1.29, 30.98]), itraconazole (6.11 [2.82, 12.67]) and caspofungin (3.80 [1.22, 10.69]). Amphotericin B was reported in three TdP cases, all with co-medications with suspected TdP liability and no significant ROR.

Among antivirals, only two agents showed a significant disproportionality: indinavir (adjusted ROR 5.31 [CI 95% 1.37, 17.15]) and nelfinavir (4.52 [2.38, 13.63]), whereas the remaining 24 antiviral molecules with TdP reports showed no disproportionality. In particular, despite a relatively high number of TdP cases, ribavirin (2 cases, all without co-medications listed by Arizona CERT), lamivudine (8 cases [2 without listed co-medications]), ritonavir (5 cases [none without listed co-medications]), zidovudine (4 cases [1 without listed co-medications]), atazanavir (4 cases [none without listed co-medications]), abacavir (3 cases [1 without listed co-medications]), stavudine (3 cases [1 without listed co-medications]) and tenofovir (2 cases [none without listed co-medications]) did not achieve a significant ROR because of the high number of non-cases.

Discussion

For marketed drugs, especially where there is high usage, the analysis of spontaneous reports is one of the most useful methods for evaluation of rare adverse events such as TdP. The FDA AERS database can be considered the largest source of these data and disproportionality detection (case/non-case methodology) has been exploited as a valuable method of identifying new signals of TdP or to confirm an already known association.[15] Moreover, because TdP is considered a DME, even a few cases with a strong causality association may be sufficient to generate a signal.[31,32] Therefore, this qualitative approach should be used in conjunction with disproportionality analysis.[22,30] Currently, only a few publications have used both qualitative and quantitative approaches in pharmacovigilance analyses.[30,33,34] In this study, we attempted to use both approaches in order to capture all possible information from spontaneous reports on TdP risk of antimicrobials.

First, the application of the case/non-case method to data of the FDA AERS database identified 17 antimicrobials associated with a significant disporportionality. Twelve of these drugs belong to classes that have been well investigated and are known to be associated with TdP (macrolides, fluoroquinolones, triazole derivative antifungals);[3,27,35-39] all these drug-event associations should be viewed as 'expected' and represent a marker of validation of the method. Notably, we consider the disproportionality associated with the remaining five drugs (linezolid, caspofungin, posaconazole, indinavir and nelfinavir) as 'unexpected', because these drugs are not mentioned by Arizona CERT. In the evaluation of these drugs the high percentage of reports with co-medications with suspected TdP liability should be considered in the assessment of causality.

For both linezolid and caspofungin, post-marketing active monitoring is currently ongoing. In particular, the FDA requested that an *ad hoc* clinical study be conducted by the manufacturer of linezolid on the risk of QT interval prolongation; this study has been completed and results are expected soon.[40] In the meantime, an analysis of the AERS database by the FDA has been performed and seven cases of electrocardiographic abnormalities were identified; however, the data are still insufficient for the US regulatory agency to make a conclusive assessment.[41] No information on QT prolongation is reported in the US labelling information for linezolid.[42]

The manufacturer of caspofungin found no evidence of QT prolongation in premarketing

studies, and the applicant undertook to conduct *ad hoc* postmarketing studies, the results of which are still unavailable.[43] The current US labelling information reports generic arrhythmias in the list of adverse reactions.[44]

Posaconazole is one of the triazole antifungals, a class that includes agents with an established risk of QT prolongation;[3] Arizona CERT does not mention posaconazole, possibly because of a lack of specific data on this agent. In fact, one TdP case was observed in premarketing trials and consequent warnings have been included in the labelling information, both in Europe and the US.[45,46]

Concerning the antiviral agents indinavir and nelfinavir, causality assessment for QT prolongation and TdP associated with this class of drugs is more complex. Even in the presence of clinical and preclinical evidence of a QT-interval prolonging potential for anti-HIV drugs,[47,48] many additional risk factors for the occurrence of TdP are frequently encountered in patients with HIV infection. Both indinavir and nelfinavir are cytochrome P450 isoenzyme inhibitors, a concern that is acknowledged in the labelling information. The US labelling information for nelfinavir also reports TdP and QT prolongation among the adverse reactions,[49] whereas the literature provides divergent data; an Italian case-control study reported an increased risk of QT prolongation, but a QT study performed by the manufacturer was negative.[47,50]

With the second approach, we identified the following additional drugs, characterized by at least two cases without co-medications with suspected TdP liability: ceftriaxone, piperacillin/tazobactam, cotrimoxazole, metronidazole, ribavirin, lamivudine and lopinavir/ritonavir. Caution is needed to interpret the meaning of these data because the nature of the database did not allow us to exclude all host-related risk factors. In our view, the low number of cases, together with the extensive experience and/or long market life of these drugs, could suggest the lack of TdP liability from their risk profile, probably with the exception of lamivudine because of the borderline ROR and 95% CI. The sensitivity of the approach could be increased by also searching for QT prolongation cases in the REACTION file of the FDA AERS.

Limitations of the Study

We acknowledge a number of limitations that should be taken into account when interpreting results obtained from spontaneous report analysis: (i) duplicates, missing data, misspelling of drug names; (ii) under-reporting; (iii) over-reporting for drugs involved in safety alerts or regulatory measures (the so-called 'notoriety bias'); and (iv) dependence of reporting rate on the length of time each drug has been on the market (the so-called 'Weber effect')[22,36,51-55] and on the time-window considered for the analysis. A wide time-window cannot verify the potential appearance or disappearance of disproportionality, but is of primary importance to capture the highest number of reports (cases and non-cases), especially for very rare adverse events such as TdP.

Moreover, small differences among RORs do not imply differences in terms of risk in clinical practice, and controversy exists as to whether comparisons of relative reporting between drugs should be made.

Drug-induced TdP is generally accepted as a multi-hit event.[3,56] Although a major risk factor has been considered in this study (i.e. concomitant use of antiarrhythmic drugs), we cannot rule out further factors that may have biased results in a way that cannot be controlled because of the nature of our source. In any case, multiple corrections or stratifications are rarely performed in pharmacovigilance studies and, in fact, they can lead to missed signals in the data-mining process.[57] The actual usefulness of multiple stratification is still debated.[58]

For drugs with high consumption, our results should be tested and integrated with additional data sources such as an electronic healthcare database, which can mitigate potential confounders. In this context, the FDA has recently announced the creation of a new integrated electronic system, named 'Sentinel', which aims to link several databases as a source for safety alert generation.[59]

Conclusions

The freely accessible version of the FDA AERS database represents an important source

of detecting potential signals of TdP, to be substantiated using different pharmacovigilance toolkits. In particular, our analysis identified five signals (linezolid, caspofungin, posaconazole, indinavir and nelfinavir), which should be further investigated and closely surveilled. These signals should be considered in evaluating the benefit-risk profile of the above drugs.

Future steps to improve the description of the TdP liability of each anti-infective drug (if possible by means of a TdP score) can consist of (i) analysing the WHO database of spontaneous reports of adverse drug reactions in order to collect further cases, in particular for drugs with higher consumption in Europe than in the US; (ii) calculating reporting rates on the basis of drug utilization data; (iii) integrating results of spontaneous report analyses with sophisticated literature evaluation, by a critical analysis of each available publication; (iv) performing basic, epidemiological (e.g. case-control study) and clinical investigations (e.g. a thorough QT study); (v) creating electronic surveillance networks (i.e. healthcare records) to prospectively monitoring safety profile of marketed drugs. The method is also applicable to other therapeutic classes of particular concern for their TdP potential (e.g. antipsychotics and antidepressants).

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