Arrhythmogenic potential of drugs

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Executive Summary: Drugs Risk Estimates and the Risk of Ventricular arrhythmia or Sudden Cardiac Death

WP5 – Analytic Database Studies

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Definitions

Partners of the ARITMO Consortium are referred to herein according to the following codes:

- **AMC:** Academisch Medisch Centrum bij de Universiteit van Amsterdam
- **AUH-AS:** Aarhus Universitets hospital, Aarhus Sygehus
- **AZ:** AstraZeneca AB
- **BIPS:** Bremen Institute Of Prevention Research and Social Medicine
- **CHARITE:** Charite - Universitätsmedizin Berlin
- **DRSU:** Drug Safety Research Unit
- **EMC:** Erasmus Universitair Medisch Centrum Rotterdam
- **FIMIM:** Fundació IMIM
- **F-SIMG:** Fondazione Scientifica SIMG-ONLUS
- **FSM-MCL:** Fondazione Salvatore Maugeri Clinica del Lavoro e Della Riabilitazione
- **LSHTM:** London School of Hygiene and Tropical Medicine
- **PHARMO:** PHARMO Coöperatie U.A
- **SGUL:** St. George's Hospital Medical School
- **SYNAPSE:** Synapse Research Management Partners SL
- **UB2:** Université Victor Segalen Bordeaux2
- **Unibo:** Alma Mater Studiorum - Università di Bologna
- **Uni-HB:** Universität Bremen
- **UNIVR:** Università Degli Studi di Verona
- **UoNEW:** University of Newcastle

Abbreviations

The following abbreviations are used in this executive summary:

- **ATC** – Anatomical therapeutic chemical classification system
- **GP** – general practitioner
- **ICD-9-CM** – International Classification of Disease, 9th rev., Clinical Modification
- **ICD-10-GM** – International Classification of Disease, 10th rev., German Modification
- **ICPC** – International Classification of Primary Care
- **IPCI** – Integrated Primary Care Information Project
- **CI** -Confidence Interval
- **UK**– United Kingdom
- **VA –** Ventricular Arrhythmia
- **WHO** – World Health Organization

Disease classification systems used by the databases

- **IPCI database** – ICPC
- **ERD database** – ICD-9-CM
- **HSD database** – ICD-9-CM
- **PHARMO database** – ICD-9-CM
- **AARHUS database** – ICD-10
- **GePaRD database**– ICD-10-GM
- **THIN database** – READ codes

Drug classification systems used by the databases

- IPCI, ERD, HSD, PHARMO, AARHUS and GePaRD database use the WHO ATC systemfor classification of drugs.
- THIN database uses BNF/Multilex which has been matched to theWHO ATC system.

1. EXECUTIVE SUMMARY

1.1 Background

In the last years, several widely used antipsychotics, antihistamines and anti-infectives have been withdrawn from the market or restricted in their use because of the risk of serious ventricular arrhythmias (VAs), such as torsades de pointes (TdP), which may lead to sudden cardiac death (SCD). The problem is still very topical, recent studies have documented an increased risk of cardiovascular death for azithromycin, thus generating concerns among regulatory agencies and health care professional with respect to the arrhythmogenic potential of this drug.

1.2 Objective

As part of the ARITMO project, we conducted retrospective, population-based, multi-database, nested case-control studies in cohorts of users of the drug class to assess in a large population from 5 European Countries the risk of VA and SCD associated with current use of individual anti-infectives (e.g. antibiotics, antimycotics, antiprotozoals and antivirals), antihistamines and antipsychotics as compared to none use.

1.3 Methods

Different drug class and outcome-specific case-control sets have been created at the site of the database custodian using dedicated standardized software, known as Jerboa©, which was originally developed in the EU-ADR project. All data were pooled on a remote research environment that is managed by Erasmus University and analysed together with all database custodians through secured remote access.
In the study on VA, data were retrieved from 7 healthcare databases (AARHUS [Denmark], GEPARD [Germany], Health-Search/Thales (HSD) and Emilia-Romagna Regional Database (ERD) [Italy], PHARMO and IPCI [Netherlands], and THIN [UK]), covering a total population of around 27 million individuals.
For SCD, data were used from 5 healthcare databases (AARHUS, HSD, ERD, IPCI and THIN), which capture information on cause of death via either GP registration or death registry.

For each individual drug class and outcome, a cohort of incident users of that drug class during a period ranging from 1997 to 2010 was identified in that database. Within this cohort all cases of VAs and SCD were identified using harmonized and validated DB-specific codes based on diagnostic codes and free-text search. Up to 100 controls were then drawn from the same source population and matched to each case by index date, sex, age and database. Exposure to study drugs was categorized into mutually exclusive groups of current (if exposure period covered the index-date plus a carry-over periods of either 7 or 30 days, depending on the drug class), recent (if exposure period ended between 7 (or 30) and 90 days before the index date), past (if the exposure period ended between 90 and 365 days before the index date), and non-use (if there was no exposure within 365 days prior to index date). We only provide estimates for those drugs with at least 3 exposed-cases to avoid instable estimates. For each drug class the odds ratio (OR) for current use for individual medications relative to non-use was estimated using multivariate conditional logistic regression while adjusting for potential confounders. In the final models we included as confounders all the known strong risk factors of VA (pre-defined) plus other weaker risk factors of VA based on modelling. Risk estimates have been reported for each database separately. Data pooling was done by using a meta-analysis of single database estimates, as well as by pooling all data together (unweighted).
In a secondary analysis that was aiming to see whether confounding by indication may have caused issues, for antibiotics, antihistamines and antipsychotics current use of amoxicillin,

cetirizine and levomepromazine, respectively, were used as secondary comparators. These drugs are known not to be associated with VA and were the most frequently prescribed in the 7 databases, as a whole. For the same three main classes several sensitivity analyses (i.e. removal of carry over from current use risk window; removal of VA cases occurring within 15 days from acute myocardial infarction) and sub-analyses (dose and duration effect) have been carried out.

1.4 Results

During a period ranging from 1997 to 2010 we identified overall 31,353cases of VA (age standardized incidence rate: 0.2 per 1000 person years) from seven healthcare databases and161,018 cases of SCD (age standardized incidence rate: 1.0 per 1000 person years) from five healthcare databases.

Antibiotics

Overall, in the unweighted pooled analysis the risk of VA could be explored for39 antibiotics (as individual ATC codes), separately. Current use of the most frequently usedpenicillins (in ranked order, phenoxymethylpenicillin, amoxicillin with enzyme inhibitor, pivmecillinam, amoxicillin, and pivampicillin), cephalosporins (cefaclor, ceftriaxone, and cefpodoxime) and macrolides (roxithromycin, clarithromycin, and azithromycin) showed a statistically significant increase in the risk of VA as compared with non-use, while no increased risk was documented for any of the fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin and moxifloxacin) and tetracyclines. However, in comparison to non-use, higher risk of VA (OR=3.6; 95%CI: 1.4-9.3) was reported for moxifloxacin in one database (ERD).Whenever possible, these findings were confirmed in the meta-analysis of single database estimates. When using current use of amoxicillin as comparator, only ceftriaxone was associated with a statistically significant increased risk of VA (OR= 3.2; 95% CI: 1.7 - 6.2).In general, no changes in the risk by different baseline cardiovascular risk or prescribed dosage were documented. Sensitivity analyses confirmed the robustness of the main findings.

Specifically, for current use of azithromycin versus non use, OR= 1.8 (95% CI: 1.3 - 2.6) was reported when using pooled data from the seven databases; however, no increase in the risk was observed when using current use of amoxicillin as comparator (OR=1.1; 95% CI: 0.7 - 1.8).

Overall, in the pooled analysis of data from five databases the risk of SCD could be explored for79 antibiotics (as individual ATC codes). The vast majority of antibiotics(including penicillins, cephalosporins, aminoglycosides, macrolides and fluoroquinolones), with some heterogeneity across different compounds, were also associated with increased risk of this outcome as compared to non-use.

Interestingly, azithromycin was not associated with an increased risk of SCD (OR= 1.0; 95%CI: 0.9-1.2) as compared to non use.

Anti-histamines

Overall, in the pooled analysis the risk of VA could be explored for 15 anti-histamines. Only current use of promethazine (OR= 1.4; 95%CI: 1.0 - 1.9) and cyclizine(OR= 5.5; 95% CI: 3.9 – 7.8) showed a statistically significant increase in the risk of VA as compared to non-use. Looking at database-specific estimates, the increased risk for promethazine and cyclizine could be documented only in PHARMO and THIN.

Removal of carry-over from the current use risk window changed the results slightly: a statistically significant increase in the risk of VA was documented now also for clemastine, whereas the risk estimates for promethazine and cyclizine increased.

Stratification by different levels of baseline cardiovascular risk did not show effect modification. No dose effects were observed.

Interestingly, loratadine was associated with a protective effect towards VA as compared to none use (OR=0.6; 95% CI: 0.4-0.8). This finding was confirmed in the meta-analysis of single database estimates.

When using cetirizine as comparator, the statistically significant increase in the risk for VA was retained for cyclizine (OR= 7.0; 95% CI: 4.1 - 11.8) but not for promethazine anymore (OR=1.3; 95% CI: 0.8 - 2.1).The risk of VA seems to be lower with longer duration of cyclizine treatment as compared to short-term use of that drug (<30 days).

Overall, in the pooled analysis the risk of SCD could be estimated for 19anti-histamines. In the pooled analysis, in addition to promethazine, cyclizine and clemastine (again only in THIN),also chorphenamine (only in THIN), alimemazine (only in THIN), cyproeptadine (only in THIN and HSD) were also associated with a statistically significant increase in the risk of SCD as compared to non-use. For all the drugs for which high VA risk was documented, a much higher risk for SCD was observed, as compared to non use.

As regards cetirizine, the increased risk was observed only in Aarhus and not in other databases which could investigate the association of this drug with SCD (THIN, HSD and ERD). As a result meta-analysis of these four databases' estimates reported no increased risk (OR= 1.1; 95% CI: 0.9-1.3), when considering random effects.

Meta-analysis of single database estimates confirmed all the other findings.

Antipsychotics

Overall, in the pooled analysis the risk of VA could be estimated for 19 antipsychotics, and, of these, 5 were atypical antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole and amisulpride). Current use of haloperidol (OR: 2.6; 95%CI: 1.9 - 3.7) and levosulpiride (OR:10.5; 95%CI: 3.1 - 35.0) was associated with a statistically significantly increased risk of VA as compared to noneuse.
Single database estimates confirmed the higher risk for haloperidol while the increase in the risk for levosulpiride was observed only in HSD.
No increasedrisk of VA could be observed for any of the atypical antipsychotics, neither in the pooled analysis nor in the meta-analysis of database-specific estimates.
The main findings were observed also in the sensitivity analyses. After removing the carry over period,an increased risk of VA was seen also for thioridazine (OR: 2.3;95%CI: 1.1 - 4.8).
For the drugs with an increased risk, a trend towards a lower risk for medium/long term use versus short term use was observed. No clear pattern was observed for different prescribed dosages and stratification by baseline cardiovascular risk score.
Overall, in the analysis of pooled data from five databases the risk of SCD could be estimated for 31 antipsychotics. In addition to haloperidol, a statistically significant increased risk of SCD was observed in a ranked (decreasing) order forlemepromazine, clotiapine, droperidol, thiapride, benperidol, clotiapine, chlorprothixene, chlorpromazine, melperone, zuclopenthixol, risperidone, promazine, sulpiride, amisulpride, olanzapine, and thioridazine.No increased risk with SCD was observed for the atypical antipsychotics quetiapine and aripiprazole.
DB-specific analysis and meta-analysis of single database estimates confirmed the main findings, except for quetiapine for which a slightly higher risk was observed in the meta-analysis (OR=1.2; 95% CI: 1.1-1.4) and amisulpride for which an increased risk was observed only in THIN but not in HSD and ERD (neither in the meta-analysis with random effect).

Antimycotics

Overall, in the pooled analysis the risk of VA could be estimated for 7 antimycotics. Among drugs with enough exposure for measuring risk estimates, no antimycotic drug was found to be

associated with VA.As regards fluconazole, an association with VA was reported only in Aarhus (OR=2.4; 95% CI: 1.1-5.1).
Overall, in the pooled analysis the risk of SCD could be estimated for 8 antimycotics. In ranked order, nystatin, ketoconazole, fluconazole and itraconazole were associated with a statistically significant increased risk of SCD as compared to non-use of any antimycotic. A protective effect was reported for terbinafine.
All these findings were confirmed in the meta-analysis of single database estimates.

Antiprotozoals
Overall, in the pooled analysis the risk of VA could be estimated for 4 antiprotozoals. Among drugs with enough exposure, chloroquine was associated with a statistically significantly increased risk of VA as compared to non-use (OR= 3.8; 95%CI: 1.5 - 9.9)**.**
Overall, in the pooled analysis the risk of SCD could be estimated for 4 antiprotozoals. Current use of metronidazole (OR= 3.0; 95%CI: 2.5 - 3.6) and quinine (OR= 1.2; 95%CI: 1.1-1.3),but not of cloroquine (OR= 1.2; 95%CI:0.6-2.5), was associated with a significantly increased risk of SCD as compared to non-use. As regards quinine the increased risk could be documented only in THIN.

Antivirals
Overall, in the pooled analysis the risk of VA could be estimated only for 3 antivirals (acyclovir, amantadine and valaciclovir). Current use of these drugs did not show any statistically significant association with the outcome.
Overall, in the pooled analysis the risk of SCD could be estimated for 6 antivirals (in addition to the three above mentioned drugs, ribavirine, famciclovir and brivudine).Only current use of amantadine (OR= 4.4; 95%CI: 1.9 – 10.4) and aciclovir (OR= 1.5: 95%CI: 1.2 - 2.0) was significantly associated with an increased risk of SCD as compared to non-use.
An increased risk of SCD with current use of amantadine could be observed only in GePARD. The meta-analysis of single database estimates (random effects) confirmed the increased risk of SCD for acyclovir.

1.5 Conclusions

This large database network from 5 European Countries allowed for investigation of the arrhythmogenic potential of many individual anti-infectives, antihistamines and antipsychotics. Results obtained in the ARITMO study confirmed the arrhythmogenic potential of several individual antibiotics, antihistamines and antipsychotics that are known to have a torsadogenic risk. For some other known torsadogenic drugs an association with VA/SCD could not be documented due to limited statistical power or effects of risk minimization activities in clinical practice. The recent evidence showing an increased risk of cardiovascular death due to arrhythmias in patients treated with azithromycin as compared with non-use was confirmed in our study, however when we compared it with current use of amoxicillin no association was observed, which indicates potential confounding by indication. On the other hand, we found no increase in the risk of SCD, specifically, and in the sensitivity analysis in which the risk of VA was compared to current use of amoxicillin, which isin line with a very recently published Danish study that explored the same association.
In general, combination of 7 electronic health record and claims databases from 5 European Countries increased substantially for each class the number of individual agents that could be investigated.

