Association of azithromycin and ventricular arrhythmia: the ARITMO project

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Background: A recent US study showed an increased risk of cardiovascular death following use of azithromycin as compared to amoxicillin. A subsequent Danish study did not confirm this association, while using penicillin V as comparator. **Objectives:** This population-based, multi-country, nested case-control study was aimed to evaluate the risk of ventricular arrhythmia (VA) with azithromycin use. **Methods:** Data source was a network of 7 healthcare databases (AARHUS/Denmark, GEPARD/Germany, HSD and ERD/Italy, PHARMO and IPCI/Netherlands, and THIN/UK), covering a population of around 35 million European subjects from 1996 to 2010. In a cohort of antibiotic users, VA cases were identified through validated coding algorithms and matched to up to 100 controls by index-date (ID, i.e. date of VA onset), sex, age and database. Exposure to azithromycin and other antibiotics was categorized as: a) current (exposure at ID or within 7 days prior); b) recent (exposure ended between 7 and 90 days prior to ID); c) past (exposure ended between 90 and 365 days prior to ID); and d) no-use (no exposure within 365 days prior to ID). Odds ratio (OR) of current use of azithromycin relative to either no-use of any antibiotic or current use of amoxicillin was estimated using multiple conditional logistic regression, while adjusting for confounders. Risk estimates were reported for each database and for pooled data. **Results:** Overall, 13,536 VA cases were identified, and, of these, 30 were currently exposed to azithromycin and 1,026 to other antibiotics. As compared to no-use of any antibiotic, current use of azithromycin (ORadj: 1.97; 95%CI: 1.35-2.86) was associated with a statistically significant increase in VA risk. In comparison to current use of amoxicillin, this risk disappeared (ORadj: 0.90; 95%CI: 0.48-1.71). Results from meta-analyses of database-specific estimates confirmed results from pooled analysis. **Conclusion:** The increase in VA risk with azithromycin was not confirmed in this European multi-database study. The observed increase in the VA risk for azithromycin, as compared to no-use, points towards confounding by indication due to acute effects of infections. **Funding:** The current study was funded by the Health Area of the European Commission under the VII FrameworkProgram (FP7/2007–2013) under Grant agreement no. 241679-theARITMO project.