Use of antibiotics and risk of ventricular arrhythmia: a nested case-control multi-database study in 5 European Countries

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Background

Some antibiotics (i.e. macrolides or fluoroquinolones) are known to be associated with cases of ventricular arrhythmia (VA). A recent study showed an increased risk of cardiovascular death in association with azithromycin, confirming the arrhythmogenic potential of macrolides[1].

Objective

Aim of this multi-database nested case-control study was to evaluate the risk of VA in current users of antibiotics (especially those known to be torsadogenic) as compared with no-use, in a large population from 5 European Countries.

Methods

All data were retrieved from 7 health care databases (AARHUS/Denmark, GEPARD/Germany, HSD and ERD/Italy, PHARMO and IPCI/Netherlands, and THIN/UK), covering a population of 27 million individuals. A cohort of incident antibiotic users from 1996 to 2010 was identified from the 7 databases. Cases of VA were selected through harmonized DB-specific and validated, coding-algorithm, including validated diagnostic codes or free-text search. Up to 100 controls were matched to each case by index-date, sex, age and database. Exposure to antibiotics was categorized into 4 mutually exclusive groups: a) current (if the exposure period covered the index-date plus a 7 day carry-over period); b) recent (if the exposure period ended between 7 and 90 days before the index-date); c) past (if the exposure period ended between 90 and 365 days before the index-date); and d) no-use (if there was no exposure within 365 days prior to index-date). Drugs with at least 5 exposed cases were included in the analysis. The odds ratio (OR) of current use for individual antibiotics relative to no-use was estimated using multivariate conditional logistic regression, while adjusting for confounders.

Results

Overall, 25,952 cases and 2,594,738 matched controls were identified. Among cases, 2,298 (8.9%) were current users of antibiotics. Current use of beta-lactam antibiotics and macrolides showed higher risk of VA as compared with no-use. Current use of azithromycin ($OR_{Adj.}$ 2.12[1.62-2.77]), clarithromycin ($OR_{Adj.}$ 2.12 [95%CI:1.72-2.61]) and erythromycin ($OR_{Adj.}$1.66 [1.28-2.13]) was associated with significantly increased risk of VA ($p<0.05$). ORs from single database and meta-analyses of database-specific estimates were in line with results from the pooled analysis. Among fluoroquinolones, current use of ciprofloxacin (OR_{Adj}1.43 [1.14-1.79]) was associated with a statistically significant increased risk of VA, while moxifloxacin showed an increased, although non-significant, risk of VA ($OR_{Adj.}$1.54 [0.94-2.77]).

Conclusion

A large database-network from 5 European Countries allowed for investigation of the arrhythmogenic potential of several antibiotics. The recently documented increase in the risk of VA in current users of azithromycin was confirmed in our study.

References

1. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012;366:1881-90.