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

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Background

In the last years, some antipsychotic drugs (APDs), such as thioridazine or haloperidol, have been associated with an increased risk of serious ventricular arrhythmias (VAs) leading to regulatory actions.

Objective

Aim of this multi-database nested case-control study was to evaluate, in a large population from 5 European Countries, the risk of VA in association with individual APDs as compared to no-use.

Methods

All 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. A cohort of incident users of APDs from 1996 to 2010 was identified from the 7 databases. Cases of VA were selected through harmonized DB-specific coding algorithms 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 APDs was categorized into mutually exclusive groups of current (if exposure period covered the index-date plus a carry-over period of 30 days), recent (if exposure period ended between 30 and 90 days before the index-date), past (if the exposure period ended between 90 and 365 days before the index-date), and no-use (if there was no exposure within 365 days prior to index-date). Only those drugs with at least 5 exposed-cases were included in the analysis. The odds ratio (OR) of current use for individual APDs relative to no-use was estimated using multivariate conditional logistic regression while adjusting for confounders.

Results

Overall,1,676 cases and 164,968 matched controls were identified. Of all cases, 629 (37.5%) were currently exposed to APDs. Current use of levosulpiride ($OR_{Adj.}$12.90 [95%CI:5.41-30.68]), haloperidol ($OR_{Adj.}$ 2.70 [2.10-3.47]),chlorprothixene ($OR_{Adj.}$ 1.81 [1.11-2.93]), thioridazine ($OR_{Adj.}$1.75 [1.06-2.89]), levomepromazine ($OR_{Adj.}$1.61 [1.02-2.55]), fluopentixol ($OR_{Adj.}$ 1.61 [1.10-2.38]), quetiapine ($OR_{Adj.}$1.53 [1.18-1.98]) and olanzapine ($OR_{Adj.}$ 1.33 [1.05-1.70]) was associated with a statistically significant increased risk of VA ($p<0.05$). ORs from single database and meta-analyses of database-specific estimates were in line with those observed in the pooled analysis.

Conclusion

A large database network from 5 European Countries allowed for investigation of the arrhythmogenic potential of individual APDs. Current use of several APDs was associated to an increased risk of VA. The risk was higher for drugs with known torsadogenic potential.