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Oral Session

New old antibiotics: safety and efficacy

FLUOROQUINOLONES AND THE RISK OF SEVERE ARRHYTHMIA - A NATIONWIDE COHORT STUDY

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Objectives

Treatment with fluoroquinolones has been associated with QT prolongation, which in turn could increase the risk of *torsade de pointes*, a potentially lethal arrhythmia. However, the relationship between prolonged QT interval and *torsade de pointes* is complex and dependent on other risk factors. Thus, although fluoroquinolones may prolong the QT interval they may not increase the risk of severe arrhythmia in an unselected general population.

Methods

We conducted a nationwide cohort study in all Danish adults, aged 40 to 74 years, linking register data of filled prescriptions 1997 to 2012, causes of death, demographical data, underlying comorbidities, concurrent medications and health care use. Cox regression was used to estimate hazard ratios (HR) for serious arrhythmia (fatal and non-fatal), cardiac arrest or sudden/unattended death, comparing 199,711 episodes of fluoroquinolone use (89% ciprofloxacin) with both *no use* of antibiotics and episodes of penicillin V use (a comparator antibiotic with no pro-arrhythmic effect), matched 1:1:1 according to propensity score. Individuals who had been hospitalized or prescribed other antibiotics within 60 days prior to inclusion were excluded. Follow up was classified as current use (1-14 days from indexdate), recent use (15-30 days) and past use (31-60 days). We hypothesized that, if an acute toxic mechanism were true, an increased risk should be restricted to the periods of current use and disappear in periods of past use.

Results

A total of 333 episodes of serious arrhythmia or sudden deaths occurred during follow up, of these 98 occurred during the period of current use (39 in fluoroquinolone users, 24 in non-users, and 35 among penicillin users). The incidence rate during the period of current use in fluoroquinolone users was 5.0 per 1,000 person-years, 3.0 with no antibiotic use and 4.6 in individuals prescribed penicillin V, which corresponded to a HR of 1.68 (1.01-2.80) compared to no antibiotic use. This was most likely due to confounding-by-indication, since HR compared to individuals prescribed penicillin V was 1.10 (0.70-1.74). All HRs were attenuated in the periods of recent and past use.

There was no effect modification by sex, age group or underlying cardiac disease. However, although inference was limited due to a small number of observations, in the subgroup of individuals (n= 28,793) with concurrent treatment with drugs that are known to increase the risk of *torsade de pointes*, estimates indicated a three-fold increased risk of arrhythmia for current users of fluoroquinolones compared to users of penicillin V, HR 2.85 (0.77-10.5), (p= 0.10 from test for interaction).

Conclusions

Fluoroquinolone use was not associated with increased risk of serious arrhythmia or sudden death in a general adult population. However caution should be exerted in individuals with concurrent treatment with other QT prolonging drugs.