Association between systemic fluoroquinolone exposure and peripheral neuropathy

Study protocol

Data source and study population

The THIN database, which contains longitudinal electronic patient records extracted from over 500 general practices across the UK, will be analysed. The study population will consist of adults aged 18 years or over identified from THIN database between January 1, 1999 and December 31, 2015 issued at least one prescription of co-amoxiclav or fluoroquinolone antibiotic product with a systemic route of administration. Co-amoxiclav will be chosen so that controls are sampled from a more representative population. Cohort entry will be defined as the date of the first co-amoxiclav or fluoroquinolone prescription for systemic administration after the latest of the following criteria: start of the study period; the practices acceptable mortality recording date; the patient's 18th birthday; date of registration with a general practice + one year. Cohort exit will be defined by the earliest of the following criteria: occurrence of the outcome; deregistration from the general practice; death; date of last data collection from the general practice; end of the study period.

Study design, outcomes and control selection

A nested case control study design will be used to assess the odds of exposure versus non-exposure among cases and controls. The date of the first event occurring after cohort entry was the index date for case subjects. Incident peripheral neuropathy will be evaluated identified through incident Read codes for peripheral neuropathy recorded within the patient's primary care electronic medical record. Up to 4 controls will be randomly selected and matched to each case on age decile, gender, general practice and calendar year of cohort entry using incidence density sampling.

Exposures

Systemic exposure to fluoroquinolone antibiotics (ciprofloxacin, moxifloxacin, levofloxacin, norfloxacin and ofloxacin) and co-amoxiclav antibiotics will be measured through identified prescriptions in pre-specified risk windows prior to the index date. Fluoroquinolone and co-amoxiclav exposure will be defined as current exposure when one or more prescriptions were issued in each risk window prior to the index date. A secondary evaluation will be performed using exposure risk windows further from the index date (e.g. 31-60 days, 61-90 days and 91-180 days) for systemic fluoroquinolone exposure to better assess past exposure should any significant finding arise. Cumulative fluoroquinolone and co-amoxiclav antibiotic exposure will also be measured within each risk window.

Confounders

Analyses will be adjusted for exact age, sex and practice-level socioeconomic deprivation (inherent in the matching criteria), smoking status, body mass index (BMI), exposure to phenytoin, metronidazole and

nitrofurantoin therapy, prior history of SLE, Sjogrens syndrome, Shingles, amylodisis and Lyme disease, comorbidity including the Charlson comorbidity index.

Data analysis

Conditional logistic regression will be used to calculate odds ratios for the association between peripheral neuropathy and fluoroquinolone exposure and co-amoxiclav exposure. Tests for interaction between fluoroquinolone exposure and other significantly associated therapies will be investigated. Multiple imputation will be used to impute missing data on body mass index and smoking status using fully conditional specification, with linear regression for continuous variables and logistic regression for categorical variables with five imputations and analysed using Rubin's rules. Adjusted rate differences will be calculated for significant fluoroquinolone associations to provide an absolute measure of effect.