PHARMO Report

Seroquel safety study

Part B: Outcome study

Executive summary

Objective

- To compare the incidence rates of specific outcomes of interest between naïve users of quetiapine and naïve users of other atypical antipsychotic drugs, specifically olanzapine and risperidone.

Methods

- An inception cohort of naïve subjects starting atypical antipsychotics use in the period 2000-2009 was created using linked community pharmacy drug dispensing data and hospital admission data from the PHARMO database. Incidence rates of all cause mortality, failed suicide attempts, extrapyrimidal symptoms (EPS), diabetes mellitus (DM), hypothyroidism, acute myocardial infarction (AMI) and stroke were compared using Cox proportional hazards regression modeling.
- Stratified analyses were performed for groups with known indications from hospital admissions, and age and dose groups, as well as for effect modifiers.

Results

- Incidence rates of hospitalizations for failed suicide attempts were significantly higher among quetiapine users compared to risperidone users (HR 2.07; 95% CI 1.35-3.16) and slightly higher with olanzapine users (HR 1.32; 95% CI 0.90-1.94). This increased relative risk was not observed in the highest dose group (>0.75 DDD-equivalents). The increased relative risk in quetiapine users was more pronounced in older ages, in adherent subjects, in subjects with no prior use of antidepressants and in those with no prior use of sedatives/hypnotics. Channeling of patients with suicide ideation into the quetiapine exposed group cannot be excluded, even after exclusion of the higher proportion of subjects with recorded prior suicide attempts in this group. Stratified analyses showed that failed suicide attempt rates were higher among subjects with known indications from hospitalizations, but this did not impact on the relative risks.
- Incidence rates for EPS were significantly lower among quetiapine users compared to risperidone users (HR 0.18; 95% CI 0.13-0.24), which was most pronounced in the highest dose group. Incidence rates for EPS were significantly lower among quetiapine users compared to olanzapine users (HR 0.59; 95% CI 0.42-0.84), but not in the highest dose group (>0.75 DDD-eq). Nevertheless there was a clear dose response relationship in all exposure groups. In the youngest age groups lower relative risks were found.
- Incidence rates for DM were significantly lower among quetiapine users compared to olanzapine users (HR 0.66; 95% CI 0.44-0.97), but not compared to risperidone users (HR 0.85; 95% CI 0.57-1.25).
- Incidence rates of all cause mortality, hypothyroidism and stroke did not differ significantly between quetiapine users and risperidone or olanzapine users. The number of AMI events was too small to draw any conclusions.

Discussion

- Indications in this study were based on known indications from hospitalizations. The majority of patients had never been hospitalized and therefore lacked any indication for antipsychotic drug use. Diagnoses may also change over time when more time has passed to allow development of the full range of symptoms of the disease. Therefore no definitive conclusions can be drawn from the stratified analyses based on known indications.
- Prescribed doses of atypical antipsychotics tended to be much lower than the defined daily doses (DDD) and approved doses of the drugs. This was most extreme in the quetiapine group. These low doses may have influenced the incidence rates of the adverse events studied in this report. The use of approved doses may lead to higher incidence rates for many outcomes, but the data also indicate that failed suicide attempt rates may drop. In this study we found the distribution of prescribed doses to be unrelated to known indications
- The median duration of exposure in this cohort was only 7 months. Only 25% were exposed for a period longer than approximately 1.5 years, therefore the power to draw any conclusions about long term exposure was limited. Nevertheless, we generally found a trend towards decreasing incidence rates with longer exposures, indicating that the current study does not provide underestimated incidence rates due to short exposure. However, it cannot be excluded that this may be a 'healthy survivor' effect.
- The analyses in this report were not corrected for multiple testing. Therefore the results of especially the stratified analyses in this report should be interpreted with caution, either by adopting a lower p-value for significance, or by determining whether a result fits in the generally observed trend.
- Although the analyses were adjusted for known confounders, residual confounding from unknown characteristics may still be present.