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General Information

Key Personnel (in addition to PI):   First Name: Fabrizia
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Degree: MD
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First Name: Rohan
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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00249158 - Risperidone in the Treatment of Behavioural and Psychological Signs and Symptoms in Dementia (BPSSD): a Multicentre, Double-blind, Placebo-controlled Parallel-group Trial
NCT00249145 - Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Identifying individual factors predictive of extrapyramidal side effects (EPS) in Alzheimer's disease

Narrative Summary:
Older people with dementia represent a group at highest risk of side effects and stroke during antipsychotic use. Understanding the individual characteristics that predict response and side effects when antipsychotics are used off license to treat psychotic symptoms in dementia will be a key step towards improving safety profiles. The proposed study aims to establish if there is a clear relationship between average steady state risperidone concentration and response (reduction in psychotic symptoms)/side effect profile in patients with Alzheimer's disease, taking into account placebo and dropout.

Scientific Abstract:
Background: Individual factors that predict antipsychotic sensitivity are poorly understood in Alzheimer's disease (AD). Research which aims to further inform age and AD- specific dose adjustments and identify patient characteristics which predict response and side effects will be a key step towards improving safety profiles
Study Design: Population approach (non-linear mixed effects modelling) to investigate the relationship between average steady state risperidone concentration, clinical response (reduction in delusions and hallucinations) and extrapyramidal side effects (EPS) in psychotic AD patients.
Participants: Patients with probable or possible AD, included in the listed trials above, who have psychotic symptoms at baseline (a score of 2 or more on any item of the BEHAVE-AD psychosis subscale at screening).
Main Outcome Measure: Clinical response (25% reduction in psychotic symptoms); EPS (emergent EPS, defined as scores >3 on Simpson Angus).
Statistical Analysis: Population pharmacokinetic-pharmacodynamic models will be developed to establish the relationship between steady state risperidone concentration, and the probability of clinical response (25% reduction in psychotic symptoms) or EPS (defined by simpson angus or other motor rating scale). The analysis will take into account placebo and drop out

Brief Project Background and Statement of Project Significance:
The mechanisms underpinning antipsychotic sensitivity are poorly understood in Alzheimer's disease (AD) and research which aims to understand the relationship between inter-individual variability in pharmacokinetics (PK) and clinical outcome will help to guide dose adjustments. The population approach is a potentially useful tool in this respect as it used non-linear mixed effects modelling to establish the consistency and identify sources of variability in dose-PK and PK-response data, with the aim of making predictions about a typical person the population of interest.
Previous studies which have used a population approach to explore PK profiles of psychotropic drugs in older AD patients have produced mixed findings. For example, PK models developed using data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials for Alzheimer's disease (AD) and schizophrenia (SZ) have shown a significant effect of age on clearance of the active metabolite (9-OH risperidone) of risperidone (Feng et al, 2008), whereas inter-individual variability in olanzapine clearance was accounted for by factors other than age (gender, smoking and African-American race) (Bigos et al, 2008b). These data, and a recent publication from the Citalopram in Alzheimer's disease (CitAD) study, which showed significant and clinically relevant effects of age and gender on metabolic clearance of R- but not S-citalopram (Akil et al. 2016), serve to emphasise the importance of extending pharmacological modelling to representative older clinical populations, to meaningfully refine and optimise age- and disease- specific dose adjustments.
The proposed study would use a population approach to characterise dose-PK and PK-outcome relationships during risperidone prescribing, with the aim of using model simulations to establish the dose adjustments required to achieve a target therapeutic range, in which symptom reduction would not be accompanied by EPS.

Specific Aims of the Project:
Aims
(i) Develop a PK model for risperidone, using PK data from the above trials. The model would include CYP status and specific covariates of interest (age, gender, renal function, height, weight, smoking, race, concomitant medications (specifically CYP substrates))
(ii)Use model outputs to simulate average steady state concentration (Cav) of (risperidone and active metabolite) across the prescribed dose range in the above trials.
(iii) Develop Cav-response and Cav-EPS models, and include drop-out and placebo response
(iv) Use model predictions (taking into account covariates which contribute to inter-individual variability) to establish the whether specific doses of risperidone(0.5mg. 1mg. 1.5mg, 2mg) achieve or exceed the target concentration range.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Above trials
Inclusion as described in the trials, with the addition of the presence of psychotic symptoms (indexed by a score of 2 or more on any item of the BEHAVE-AD psychosis subscale at screening)
Exclusion criteria as described in the above trials

Main Outcome Measure and how it will be categorized/defined for your study:
Reduction in psychotic symptoms, defined by Psychosis Cluster Score of Pathology from the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)
EPS - emergent EPS will be defined as scores of 3 or more on Simpson Angus Scale

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Average steady state concentration risperidone and active metabolite

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Covariates
AGE (continuous)
GENDER
CrCL - ml/min (continuous)
Comcomitant medication (will need to be examined and categorised)
smoking status (binary)
CYP status

Statistical Analysis Plan:
Analysis will be conducted under the supervision of the London Pharmacometric Group (UCL) and will include both descriptive and population-based analysis
(i) Compartmental PK models will be used to describe the time course of plasma drug concentrations on PK parameters. A nonlinear mixed-effects model will be developed to simultaneouslydescribe risperidone and 9-OH risperidone concentration-time profile. Covariate effects on risperidone and 9-OH risperidone PK parameters will be assessed, including age, weight, sex, smoking status, race and concomitant medications. If possible (if cyp2d6 genetics are available), CL will evaluated using a mixture model, which separates [poor metabolizer (PM), extensive metabolizer (EM) and intermediate metabolizer (IM)].
(ii) The combination of an Emax and the Weibull model will be used to describe drug and placebo effects. An exponential model will be used to identify the predictors of probability of dropout. Simulations will be performed to establish target concentration to elicit a response (using 25% reduction in target symptom).
(iii) EPS will be modelled using a continuous time probability model with Markov elements, taking into account placebo and drop-out.

Project Timeline:
Start data: Aug 2016
Timelines:
Extract data /set up appropriate database /spreadsheet to model data in either Monolix or NON-MEM (1 month)
Develop PK-PD models/simulations (3 months)
Manuscript preparation/revisions (2 months)
This will be completed within 6 months

Dissemination Plan:
JAMA Psychiatry
Am J Psychiatry

Bibliography:

Feng Y, Pollock BG, Coley K, Marder S, Miller D, Kirshner M, et al. Population pharmacokinetic analysis for risperidone using highly sparse sampling measurements from the CATIE study. British journal of clinical pharmacology. 2008;66(5):629-39.

Bigos KL, Pollock BG, Coley KC, Miller del D, Marder SR, Aravagiri M, et al. Sex, race, and smoking impact olanzapine exposure. Journal of clinical pharmacology. 2008;48(2):157-65.

Akil A et al. (2016) A population pharmacokinetic model for R- and S-citalopram and desmethylcitalopram in Alzheimer's disease patients with agitation J Pharmacokinet Pharmacodyn 43:99-109
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