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17th February, 2017

Study Title: Rationalisation of antipsychotic drug use in older people, using [18]F-Fallypride PET

REC Reference: 11/SC/0486

Protocol number: 2167SR

EudraCTnumber: 2011-005218-13

Chief Investigator: Dr Suzanne Reeves

The purpose of the trial was to investigate disease-specific mechanisms underpinning antipsychotic drug sensitivity and optimise prescribing of amisulpride in Alzheimer's disease (AD) with behavioural and psychotic symptoms and Schizophrenia-like psychosis with onset after the age of 60 years (SLP).This is a single centre, non-randomised open-label trial to observe and optimise amisulpride prescribing in older patients.

This trial intended to enrol 80 patients (40 with AD and 40 with SLP), all of whom would receive amisulpride at a dose range of 50mg to 200mg; and 20 healthy participants, who would receive 50mg amisulpride for 4 days only.

In addition to the treatment component, there would also be a control group from each patients group (10 with AD and 10 with SLP) who would be assessed twice in the absence of medication.

A further group (10 patients with AD and 10 with SLP) would act as an additional 'antipsychotic-free' group, in whom image data would be collected to ensure that an age and gender corrected estimate of baseline tracer binding could be made in participants who were unable to have a pre-treatment scan.
The trial objectives were as follows:

Primary Objectives:

(i) To investigate the relationship between plasma levels and regional D2/3 receptor occupancy following steady state (4 days) treatment with a fixed dose (50mg) of amisulpride within 3 groups: Healthy controls (HC), AD and SLP (20 in each group). This will test the hypothesis that regional D2/3 receptor occupancy will be higher in the AD group than the other 2 groups, indicating increased central access of amisulpride

(ii) To investigate the relationship between plasma kinetics, regional D2/3 receptor occupancy and therapeutic and adverse effect profile in patients with SLP and AD (20 in each group) during 4-10 weeks treatment with amisulpride (50-200mg daily). This will test the hypothesis that the threshold of D2/3 receptor occupancy for a clinical response (25% reduction in symptoms) and emergence of motor side effects be lower in SLP than AD, indicative of reduced receptor reserve and/or signalling

(iii) To combine data on clinical outcome and pharmacokinetics in patients with SLP and AD (40 in each group) during 4-10 weeks treatment with amisulpride (50-200mg daily). This will determine the minimal clinically effective dose, optimal dose range required to produce symptom reduction without side effects.

Secondary objective

To test the hypothesis that attentional/executive functioning will improve and motor speed decrease between baseline and end of dose-titration in the 2 patient groups (4-10 weeks).

Primary endpoints

(i) D2/3 receptor occupancy following steady state (4 days) treatment with amisulpride 50mg daily (groups 1,2)

(ii) D2/3 receptor occupancy, symptom reduction, motor side effect score at the end of dose-titration (4-10 weeks of 50-200mg amisulpride) (group 3)

Secondary endpoints

(i) Change in neuropsychological test performance measures at the end of dose titration (4-12 weeks treatment with 50-200mg amisulpride) (groups 2 and 3)

(ii) Change in test performance measures over a 4 week period in the absence of treatment (group 4)

Progress of the study

Recruitment period

June 2012-June 2015

64 participants recruited

Group 1 (healthy controls) not recruited

Group 2 (not recruited)

Group 3 (AD, SLP treated group): 32 AD, 8 SLP

Group 4: 14 (9 AD, 5 SLP, neuropsychological testing twice to inform on within-subject variability on tests which would be used as secondary outcome measures in the study)

Group 5: 10 (all AD, imaged once)

Treated group

AD group

32 recruited (13 men, 19 women; mean +-SD age 82+-7 years; MMSE 17+-5)

7 withdrawn prior to data collection:

1 (man) excluded after being diagnosed with motor neurone disease

3 (2 men, 1 woman) withdrawn after refusing to comply with study procedures

1 (man) withdrawn due to death before starting treatments (urinary tract infection)

2 (women) withdrawn before blood sampling could be completed (falls)

Of the 25 participants who were treated with amisulpride, blood concentration (40.9+-27.1ng/ml) was taken during steady state treatment with 25-75mg/day. During amisulpride dose titration, 7 (25%) patients were withdrawn, due to clinically significant extrapyramidal side effects (Simpson Angus Scores >6) (n=5), falls (n=1), and unrelated health problems (n=1). Subclinical extrapyramidal side effects (Simpson Angus Scale scores 3-5), which did not lead to treatment cessation, emerged in 2 patients. There were 6 SAEs (one prior to starting medication). All who completed the study (n=18) were prescribed 50mg/day amisulpride and had achieved a mean reduction in symptom scores of 80 ± 27% (delusions), 95 ± 15% (hallucinations) and 84 ± 28% (agitation). Imaging included baseline [^{18}F]fallypride imaging (n=2), and post-treatment data (n=16)

SLP

8 recruited (6 women; 76 ± 6 years)

2 withdrawn due to non-compliance/disengagement

Of the 6 who complied with treatment, blood concentration (69.5+-34.9 ng/ml) was taken during steady state treatment with 50-100mg/day. There was a 74 ± 12 % reduction in symptom scores (76 ± 15%, unusual thought content; 68% ± 20%, suspiciousness; and 69% ± 34%, hallucinations), with complete resolution of symptoms in 2 patients. Subclinical extrapyramidal side effects emerged in 2 which led to dose reductions and 1 was withdrawn due to syndrome of inappropriate antidiuretic hormone secretion, (SIADH), which was reported as a SUSAR. There were no SAEs. Imaging included baseline [18F]fallypride imaging data (n=5) and post-treatment imaging (n=4)

Trial termination

The trial terminated early due to failure to achieve recruitment targets. The last patient last visit was on 5th June 2015. The end of trial notification was submitted to MHRA and Research Ethics Committee at the end of February 2016. The study was powered on the basis of imaging and aimed to detect differences in the threshold occupancy for extrapyramidal side effects (EPS) during dose titration in the

2 patient group. From the protocol: *'Based on the SD (4%) of the mean threshold striatal D2/3 occupancy for EPS in young adults, a sample size of 20 in each group will allow a difference of 3.6% to be detected'*. As you are aware, group 5 (antipsychotic free control group) was included as part of a substantial amendment, given the difficulties encountered when trying to obtain imaging data over many months, which led to very small numbers of people who were imaged pre-treatment

Analysis

As the study was not able to directly compare imaging data in the 2 groups (given the small sample size of the SLP group), we were unable to report on primary or secondary objectives. As a result, we were required to combine data from the AD clinical dataset with a richly sampled phase I study (supplied by Sanofi) on 20 healthy elderly participants (age 65-79 years), each sampled 14 times during the first 72 hours following a single 50mg dose of amisulpride. Enriching the sample meant that it was possible to develop a pharmacokinetic model for amisulpride in older people and make predictions about dose-concentration relationships. A manuscript was accepted for publication in *Psychopharmacology* which described dose-concentration relationships and suggested that age and weight-based dose stratification should be considered for use in older people with AD (see attached manuscript), with the following Abstract:

Current prescribing guidelines for the antipsychotic amisulpride are based largely on pharmacokinetic (PK) studies in young adults, and there is a relative absence of data on older patients, who are at greatest risk of developing adverse events. This study aimed to develop a population PK model for amisulpride specifically in older people, by combining data from a richly sampled phase 1, single (50mg) dose study in healthy older people (n=20, 65-79 years), with a clinical dataset obtained during off label, low dose (25-75mg daily) amisulpride prescribing in older people with Alzheimer's disease (AD) (n=25, 69-92 years), as part of an observational study. After introducing a scaling factor based on body weight, age accounted for 20% of the inter-individual variability in drug clearance (CL), resulting in a 54% difference in CL between those aged 65 and those aged 85 years, and higher blood concentrations in older patients. These findings argue for the consideration of age and weight-based dose stratification to optimise amisulpride prescribing in older people, particularly in those aged 85 years and above.

A second manuscript, which extended model development to include imaging data was accepted by *Brain* (see attached) with the following Abstract:

Antipsychotic drugs, originally developed to treat schizophrenia, are used to treat psychosis, agitation and aggression in Alzheimer's disease. In the absence of dopamine D2/3 receptor occupancy data to inform antipsychotic prescribing for psychosis in Alzheimer's disease, the mechanisms underpinning antipsychotic efficacy and side effects are poorly understood. This study used a population approach to investigate the relationship between amisulpride blood concentration and central D2/3 occupancy in older people with Alzheimer's disease by combining (i) Pharmacokinetic data (280 venous samples) from a phase I single (50mg) dose study in healthy older people (n=20, 65-79 years) (ii) Pharmacokinetic, [18F]fallypride D2/3 receptor imaging and clinical outcome data on patients with Alzheimer's disease who were prescribed amisulpride (25-75mg daily) to treat psychosis as part of an open study (n=28; 69-92 years; 41 blood samples, five pre-treatment scans, 19 post-treatment scans) (iii) [18F]fallypride imaging of an antipsychotic free Alzheimer's disease control group (n=10, 78-92 years), to provide additional pre-treatment data. Non-linear mixed effects modelling was used to describe pharmacokinetic-occupancy curves in caudate, putamen and thalamus. Model outputs were used to estimate threshold steady state blood concentration and occupancy required to elicit a clinically relevant response (>25% reduction in scores on delusions, hallucinations and agitation domains of the Neuropsychiatric Inventory) and extrapyramidal side-effects (Simpson Angus Scale scores >3). Average steady state blood levels were low (71+-30 ng/ml), and associated with high D2/3 occupancies (65+-8%, caudate; 67+-11%, thalamus; 52+-11%, putamen). Antipsychotic clinical response occurred at a threshold concentration of 20ng/ml and D2/3 occupancies of 43% (caudate), 25% (putamen), 43% (thalamus). Extrapyramidal side effects (n=7) emerged at a threshold concentration of 60ng/ml, and D2/3 occupancies of 61% (caudate), 49% (putamen) and 69% (thalamus). This study has established that, as in schizophrenia, there is a therapeutic window of D2/3 receptor occupancy for optimal treatment of psychosis in Alzheimer's disease. We have also shown that occupancies within and beyond this window are achieved at very low amisulpride doses in Alzheimer's disease due to higher than anticipated occupancies for a given blood drug concentration. Our findings support a central pharmacokinetic contribution to antipsychotic sensitivity in Alzheimer's disease and implicate the blood brain barrier, which controls central drug access. Whether high D2/3 receptor occupancies are primarily accounted for by age- or disease-specific blood brain barrier disruption is unclear, and this is an important future area of future investigation, as it has implications beyond antipsychotic prescribing.

A third manuscript, which is *In Press in J Clinical Psychiatry* extended model development to outcome data (see attached manuscript), with the following Abstract:

Objective

We have previously reported high dopamine D2/3 receptor occupancies at low amisulpride concentrations in older people with Alzheimer's disease (AD), during off label treatment of AD-related psychosis. This study explored pharmacokinetic (PK) (concentration) and pharmacodynamic (PD) (prolactin, D2/3 occupancy) contributions to symptom reduction and extrapyramidal side effects (EPS), to inform AD-specific dose adjustments.

Methods

Population PK-PD models were developed by combining PK data from a phase 1 study in healthy older people, with PK prolactin, [18F]fallypride D2/3 receptor imaging, and clinical outcome data from older patients prescribed open amisulpride (25-75 mg/day) to treat AD-related psychosis. Model predictions were used to simulate dose-response and dose-EPS.

Results

Symptom reduction (Delusions) was associated with amisulpride concentration ($p = 1.3e-05$) and D2/3 occupancy ($p<0.01$, caudate, putamen, thalamus). Model predictions suggested that, across concentrations of 40-100ng/ml, and occupancies of 40-70% in caudate and thalamus, and 30-60% in the putamen, there was a 50-90% probability of response and <30% probability of EPS. Simulations, based on concentration-delusions and concentration-EPS model outputs, showed that 50 mg/day amisulpride was the appropriate dose to achieve this target range in those aged >75 years: Increasing the dose to 75 mg/day increased the risk of EPS, particularly in those aged >85 years of low body weight.

Conclusion

These findings argue strongly for the consideration of age and weight-based dose adjustments in older patients with AD-related psychosis, and indicate that 50 mg/day amisulpride may be both the minimal clinically effective dose and, in those aged >75 years, the maximally tolerated dose.

Dissemination/feedback

The findings of these papers were presented to an Alzheimer's Society focus group, who are strongly supportive of future studies of this nature, which include serial blood sampling, to optimise dose predictions. The findings have been presented as a poster at an international conference (European College of Neuropsychopharmacology (ECNP Amsterdam 2015), to ~850 people as part of the 2106 Neuroscience symposium (UCL, London), and are now part of a British Association for Psychopharmacology (BAP) module at which I teach annually. The therapeutic window of occupancy is

available on social media (tweeted by Brain). Plans are being made to feedback the findings to clinicians and carers at KCL/SLaM before data are archived.

Yours Sincerely

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