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Protocol for a randomised controlled trial: efficacy of donepezil against psychosis in Parkinson's disease (EDAP)

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ABSTRACT

Introduction: Psychosis, including hallucinations and delusions, is one of the important non-motor problems in patients with Parkinson's disease (PD) and is possibly associated with cholinergic neuronal degeneration. The EDAP (Efficacy of Donepezil against Psychosis in PD) study will evaluate the efficacy of donepezil, a brain acetylcholine esterase inhibitor, for prevention of psychosis in PD.

Methods and analysis: Psychosis is assessed every 4 weeks using the Parkinson Psychosis Questionnaire (PPQ) and patients with PD whose PPQ-B score (hallucinations) and PPQ-C score (delusions) have been zero for 8 weeks before enrolment are randomised to two arms: patients receiving donepezil hydrochloride or patients receiving placebo. The patients are then followed for 96 weeks. The primary outcome measure is the time to the event, defined as getting 2 points or more on the PPQ-B score or PPQ-C score, which is assessed using a survival time analysis. The hypothesis being tested is that donepezil prevents psychosis in patients with PD. Efficacy will be tested statistically using the intention-to-treat analysis including a log-rank test or Cox proportional hazard models. Secondary outcomes, such as changes of PPQ scores and Unified Parkinson's Disease Rating Scale scores from baseline will be assessed.

Ethics and dissemination: Ethics approval was received from the Central Review Board of the National Hospital Organization, Tokyo, Japan. The trial was declared and registered to the Pharmaceuticals and Medical Devices Agency(PMDA), Japan (No. 22-4018). All participants will receive a written informed consent that was approved by the Central Review. A completed written informed consent is required to enrol in the study. Severe adverse events will be monitored by investigators and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA.

Clinical Trial Registration Number: UMIN000005403.

ARTICLE SUMMARY

Strengths and limitations of this study

- In previous randomised controlled trials for psychosis the efficacy was investigated in patients who presented with psychosis and the primary endpoint was improvement of psychotic symptoms. By comparison, this study is designed to evaluate the prophylactic effect in patients without current psychosis. Because psychosis may be overlooked and underestimated it is assessed using a questionnaire, Parkinson Psychosis Questionnaire (PPQ) every 4 weeks.
- The strength of this study is its prospective design using the preset definition of psychosis using PPQ (hallucinations/illusion and delusions). However, it could also be a limitation; because other types of psychosis cannot be evaluated.
- Another limitation is the sample size estimation. Because there have never been any randomised trials for the prevention of psychosis, previous data for sample size estimation were insufficient. To resolve this issue we estimated the sample size based on our previous retrospective cohort study.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder presenting with motor disturbances, including muscular rigidity, tremor, bradykinesia or postural reflex disturbance. These motor symptoms are caused by the depletion of dopamine in the striatum. Dopamine replacement therapy can improve motor disturbances in PD. However, many patients suffer from psychiatric symptoms, such as hallucinations and delusions, during their long therapy process.[1 2]

In previous studies the efficacy of antidopaminergic drugs, including clozapine,[3 4] olanzapine,[5] quetiapine[6 7] and risperidone,[8] was investigated based on the possibility that psychosis may be caused by excessive dopamine replacement therapy. Although the efficacy of clozapine against psychosis without worsening of motor symptoms of PD was established in the French Clozapine Parkinson Study[4] and the PSYCHOPLOS study,[4] clozapine has a risk of granulocytopenia and requires careful

blood cell monitoring. Previous randomised clinical trials (RCTs) demonstrated that olanzapine improves psychosis, but there were no significant differences in improvement between the olanzapine groups and the placebo groups. In addition, olanzapine worsened motor symptoms in PD compared with placebo.[5] Two other RCTs demonstrated that quetiapine does not worsen motor symptoms; however, its efficacy against psychosis was not superior to placebo.[6 7] A small-sized RCT comparing risperidone and clozapine demonstrated that risperidone improves psychosis as well as clozapine; however, risperidone worsened motor symptoms.[8] There have been no clinical trials regarding other antipsychotic drugs against psychosis in PD. Taken together antidopaminergic drugs, except for clozapine, insufficiently improve psychosis.

Cholinergic neurons of the basal forebrain play an important role in cognitive function and disruption of the cholinergic system has been proposed in Alzheimer's disease.[9 10] Previous reports demonstrated that the cholinergic neurons are degenerated, as are dopaminergic neurons in PD,[11] suggesting the possibility that psychosis could be caused by cholinergic neuronal damage, but not by dopaminergic replacement therapy.[12]

Previously we investigated the clinical risk factors for psychosis in a retrospective cohort study (unpublished data). In this study, 334 patients with PD were followed until the occurrence of psychosis in 24 months. PD psychosis was significantly associated with the severity of PD, PD duration and cognitive function. These data demonstrated that psychosis is associated with the severity of the disease and cognitive function and the results are very consistent with previous reports.[13–15] In addition, the influence of medications was analysed using a case-crossover study comparing medications at the endpoint (occurrence of psychosis or end of the study) and those for 1 or 3 months before the endpoint, and the analysis showed that the use of anticholinergic drugs was a significant risk factor for psychosis. In these results psychosis may have been caused by the degeneration of cholinergic neurons and deterioration of cognitive function.

Donepezil hydrochloride is an inhibitor of acetylcholine esterase in brain neurons[16–18] and activates cholinergic neurons.[16 19 20] Manganelli *et al*[21] have demonstrated, by using a neurophysiological technique, the short latency afferent inhibition, a functional involvement of central cholinergic circuits in patients with PD with visual hallucinations. In this context donepezil could reduce the risk of psychosis in patients with PD. In this study we will investigate the efficacy of donepezil against psychosis in a multicentre double-blinded placebo-controlled study.

Except for clozapine, in previous placebo-controlled RCTs against psychosis, the ratio of participants who dropped out from the trials was relatively high, ranging from 18%[5] to 50%.[7] A high drop-out ratio may be due to patients' worry about being assigned to placebo. In addition, psychosis may spontaneously improve even if assigned to placebo. These conditions make it difficult to demonstrate significant differences between active drugs and placebo. Therefore, in this study, the main outcome measure is the prophylactic efficacy of donepezil and the efficacy will be analysed using a survival time analysis.

Because psychosis may be overlooked and underestimated, it is assessed using Parkinson Psychosis Questionnaire (PPQ)[22] given every 4 weeks. The PPQ consists of four categorical dimensions: sleep disturbance, hallucinations/illusions, delusions and orientations. Eligible patients are those whose scores on the PPQ-B (hallucinations/illusion) and PPQ-C (delusion) are zero at least for 8 weeks before enrolment and the primary endpoint is the occurrence of psychosis that is defined as PPQ-B ≥2 or PPQ-C ≥2, because the situations when PPQ-B or PPQ-C is ≥2 can result in clinically harmful conditions.

To exclude patients with dementia with Lewy bodies (DLB) and PD with dementia, patients with Minimental State Examination (MMSE) score less than 24 are excluded. The risk of psychosis is low in patients with an H-Y stage of 2 or less and the evaluation of psychosis is difficult in patients with H-Y stage of 5. Therefore, patients with H-Y stage of 1−2 or 5 are excluded. The length of time to the occurrence of psychosis is compared between participants who were prescribed placebo and those who were prescribed donepezil.

Hypothesis to be examined in the study

Psychosis may be caused by dysfunction of brain cholinergic neurons. We examine the hypothesis that donepezil prevents psychosis in patients with PD.

METHODS AND ANALYSIS

Study design

A multicentre, double-blinded, placebo-controlled, randomised trial. A two arm study.

Sites where the study is performed

Eight hospitals of the National Hospital Organization: Utano National Hospital, Hokkaido Medical Center, Sagamihara National Hospital, Shizuoka Institute of Epilepsy and Neurological Disorders, Kyoto Medical Center, Minami Kyoto Hospital, Toneyama National Hospital and Nagasaki Kawatana Medical Center.

Eligibility criteria

Eligibility

Eligible patients are those who satisfy all of the following criteria and who do not have any of the listed exclusion criteria.

Inclusion criteria

1. PD: Diagnosis of PD according to steps 1 and 2 of the United Kingdom Brain Bank Parkinson's Disease Diagnostic Criteria.[23]

2. Modified H-Y grades from 2.5 to 4.0, in 'ON' period if patients suffer from motor fluctuation.
3. Psychosis: During the 8 weeks before the study enrolment (visit 2, V2), there has been no evidence of psychosis that is defined in the PPQ; the answers to questions B (hallucinations/illusions) and C (delusions) are none (score 0) at V1 and V2.
4. Cognitive function: The score on the MMSE is 24 or more at V1 and V2.
5. Either inpatients or outpatients.
6. Sex: Men and women can be enroled. Women of childbearing age can be enroled if a pregnancy test is negative and she agrees to avoid getting pregnant during the study.
7. Age: Patients are between the ages of 20 and 79 years (inclusive) when giving consent.
8. The purpose and methods of the trial are explained and a written informed consent is obtained.
9. Patients who can follow the protocol, will consent to examination and will provide information on their symptoms.

Exclusion criteria

1. Patients who have previously taken donepezil hydrochloride.
2. Patients who took the following anticholinergic drugs in the preceding 4 weeks before V2: trihexyphenidyl, biperiden, profenamine, piroheptine, metixene, mazaticol, promethazine or cyproheptadine.
3. Patients who took Tsumura No. 54 (Yoku-Kansan) in the preceding 4 weeks before V2.
4. Patients who took antipsychotics in the preceding 12 weeks before V2.
5. Patients who fulfil the criteria of probable DLB according to the revised criteria for the clinical diagnosis of DLB in the third report of the DLB consortium.
6. Patients who have previously been diagnosed with schizophrenia.
7. Patients who have previously had stereotactic brain surgery.
8. Patients who are or were allergic to piperidine derivatives.
9. Patients with severe hepatic or renal dysfunction.
10. Patients with sick sinus syndrome or cardiac conduction block in the atrium or of the atrioventricular junction (sinoatrial block or AV block of 2° or more).
11. Patients with present or past severe bronchial asthma, severe peptic ulcer or severe obstructive pulmonary disorders.
12. Patients with bradycardia <45/min in ECG at V1.
13. Patients with a QTc >460 ms in ECG at V1.
14. Patients who are pregnant.
15. Patients who participated in other clinical trials in the 12 weeks before V2.
16. Patients who are diagnosed with a malignancy.
17. Patients who are judged as inappropriate for the study.

Concomitant medications and restricted medications

During the study period the following drugs are not permitted:

1. Central anticholinergic drugs.
2. Antipsychotic drugs.
3. Inhibitors of brain acetylcholine esterase.
4. *N*-methyl-D-asparate receptor antagonists.
5. Tsumura kampo medicine No. 54 (Yoku-Kansan).
6. Study drugs except for the efficacy of donepezil against psychosis in PD (EDAP) study drug.

Definition of psychosis

In this study, psychosis is monitored every 4 weeks using the PPQ-B (hallucinations/illusions) and PPQ-C (delusions). In determining the cut-off points for PPQ-B and PPQ-C, we think that the lower threshold (or mild psychosis) is better for this trial because of the following three reasons: (1) a lower threshold will allow for higher statistical power in the limited-size trials; (2) higher threshold (or severe psychosis) will make the interpretation of the trial results difficult because investigators will reduce dopaminergic drugs even if mild psychosis occurs, prior to worsening of psychosis; (3) a higher threshold is difficult to set because of the concern over safety of the participants (severe psychosis will be documented as a severe adverse event in the trial). A condition where the PPQ-B or PPQ-C score is 2 or higher is harmful to daily living. A condition with PPQ-B or PPQ-C ≥1 would not always be harmful to daily living and may also be encountered under healthy conditions. Therefore, in this study, psychosis is defined as PPQ-B or PPQ-C ≥2.

The first occurrence of psychosis

To specify the date of the first occurrence of psychosis, patients and their caregivers are requested to fill a diary on visual or auditory hallucinations or illusions. If the date of the occurrence of psychosis cannot be specified by the diary, midpoint between the last visit and the current visit will be regarded as the date of psychosis occurrence.

Sample size calculation

In our previous study that followed patients with PD, about 20% patients required antipsychotic medications because of psychosis that was defined as the use of antipsychotics (unpublished data). In the EDAP trial the definition of psychosis is defined according to the PPQ-B (hallucinations/illusions) and PPQ-C (delusions) because of a high inter-rater reliability of the PPQ. According to the definition of psychosis in this study (PPQ-B ≥2 or PPQ-C ≥2), we assumed the cumulative occurrence of psychosis as 45% in the placebo group. According to the previous study, the use of donepezil hydrochloride will reduce the risk of psychosis occurrence by 0.5, and therefore, the cumulative occurrence of psychosis would be 22.5% in the active group. The sample size was calculated on the condition that α is 0.05 (bilateral), power is 0.8 and the statistical test is the

log rank test. The sample size was calculated as 84 in each group and 142 in the total participants.

Allocation

Eligibility is checked at V1 according to inclusion and exclusion criteria. Additionally, scoring of PPQ-A–D is performed at V2 and we will confirm eligibility, including that the PPQ-B as well as the PPQ-C scores are 0 at V2. The allocation will be carried out with stratification of the subjects according to sex (male and female) and modified H-Y (2.5–3.0 and 4.0), because the rate of psychosis is associated with sex and H-Y grades.

Observations

V1 screening—At V1 the following tests or examinations will be performed:

1. PPQ
2. Modified H-Y
3. MMSE
4. Peripheral blood sampling, urine analysis and ECG
5. Urine human chorionic gonadotropin pregnancy test if the participant is non-menopausal or within 1 year from menopause
6. Body weight, height
7. Onset of PD, history of hallucinations, delusions or impulse control disorders
8. Smoking

V2 enrolment—At V2 the following tests and examinations will be performed:

1. PPQ
2. Epworth Sleeping Score (Japanese version)
3. Unified Parkinson's Disease Rating Scale (UPDRS) I, II, III and IV

The following examinations will be performed between V2 and V3:

1. Frontal lobe Assessment Battery (FAB)
2. Revised version of Wechsler Memory Scale (WMS-R)

The following examinations will be performed limited to participants from Utano National Hospital between V2 and V3:

1. EEG
2. Cerebral blood flow scintigram using ^{123}I-amphetamine
3. MRI volumetry of the brain

V3—At V3 the study drug (3 mg) will be prescribed.

V4—At V4 PPQ will be examined. Study drug (5 mg) will be prescribed after confirming safety.

V5—At V5 the following tests and examinations will be performed:

1. PPQ
2. UPDRS-III, and modified H-Y
3. JESS
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required

At V6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 PPQ can be performed by telephone interview.

At V7, 11, 13, 17, 19, 23, 25 following tests will be carried out:

1. PPQ
2. UPDRS-III and modified H-Y
3. JESS
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required

At V9, 15, 21 the tests performed are as follows:

1. PPQ
2. UPDRS-III, and modified H-Y
3. JESS
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required
5. MMSE, FAB, WMS-R

At V27 the following tests will be carried out:

1. PPQ
2. UPDRS-I, II, III, IV and modified H-Y
3. JESS
4. Peripheral blood sampling, urinary analysis, ECG. Urinary pregnancy test if required
5. MMSE, FAB, WMS-R

Apolipoprotein genotype will be examined if the participant gives consent for the genotyping, because the ε4 genotype may reduce the efficacy of donepezil in Alzheimer's disease.

Compliance rate of the investigational product will be monitored at every visit. Dose of drugs prescribed (including drugs for PD and other medical conditions) will be collected at every visit.

Study period and definition of endpoint

The study period is from the start of administration of the investigational product (donepezil or placebo) to the endpoint and the longest observation period is 96 weeks.

Endpoint is the occurrence of psychosis or termination of observation. Psychosis is defined as a score of 2 or more on the PPQ-B or PPQ-C (if any answer to questions in PPQ-B or PPQ-C is yes and the frequency or the severity is 2 or more) that is shown in the yellow area in table 1.

Primary outcome measure and statistical analysis

Primary outcome measure is the time to the occurrence of psychosis from V2 during 48 weeks. The time length to the occurrence of psychosis will be compared between the placebo and the donepezil groups and the difference will be statistically examined using the log rank test. Kaplan-Meier survival curves will be obtained from the data of the placebo and donepezil groups.

Secondary outcome measures

The following data will be obtained and compared between the placebo and donepezil groups as secondary outcome measure:

Table 1 Multiplicative Parkinson Psychosis Questionnaire score

	Frequency		
Severity	**Up to once per week**	**Several times per week**	**Once or more per day**
A. Early symptoms/sleep disturbance			
Not or slightly affecting well-being	1	2	3
Moderately affecting well-being	2	4	6
Severely affecting well-being	3	6	9
	Only during the night	During the night and occasionally during the day	Almost every day and night
B. Hallucinations/illusions			
Insight retained	1	2	3
No full insight	2	4	6
Lacking insight	3	6	9
	Up to once per week	Several times per week	Once or more per day
C. Delusions			
Without affecting the social environment	1	2	3
Affecting the patient by emotional distress	2	4	6
Affecting the patient by accusation, aggression or lack of cooperation	3	6	9
D. Orientation			
No requirement of supervision	1	2	3
Temporal requirement of supervision	2	4	6
Permanent requirement of supervision	3	6	9

1. Time to the occurrence of the first psychosis from V2 during 24 weeks.
2. The proportion of participants with psychosis to total participants. The comparison will be analysed using a statistical model.
3. PPQ score and the changes of MMSE, WMS-R, FAB from the baseline at V9.
4. PPQ score and the changes of MMSE, WMS-R, FAB from the baseline at V15.
5. PPQ score and the changes of MMSE, WMS-R, FAB from the baseline at V21.
6. PPQ score and the changes of MMSE, WMS-R, FAB from the baseline at V27.
7. Subgroup analysis of the primary and secondary outcome measures by genotype of apolipoprotein E.
8. Secondary measure limited to Utano National Hospital
   A. I^{123}-iodo-amphetamine brain scintigram at the endpoint. The comparison will be performed by a 3D-SSP method.
   B. The grand total score of EEG at the endpoint.

Safety

Patients will be requested to report any adverse events. All adverse events that are still present must be followed up until their disappearance or until no further requirement of follow-up. Severe adverse events will be monitored by investigators and in cases where a severe adverse event was previously unreported, it will be reported to the PMDA. To detect QT time elongation ECG will be performed every 8 weeks. Complete blood cell count and laboratory data including hepatic and renal functions will be tested every 8 weeks.

ETHICS AND DISSEMINATION

According to 'Good Clinical Practice (GCP)' released by the Ministry of Health, Labor and Welfare, all participants will receive a written informed consent that is approved by the Central Review. A completed written informed consent is required to enrol in the study.

Severe adverse events will be monitored by investigators. All severe adverse events will be reported to all investigators through a web-based electric data capturing system and be discussed. In cases where a severe adverse event was previously unreported, it will be reported to the PMDA according to the GCP guideline. The trial was registered in UMIN Clinical Trials Registry (UMIN-CTR; UMIN000005403).

The key-code table that contains allocation data is generated by a key-holder who will not participate in the study, using a computer programme. It is concealed from other personnel until key-opening by the key-holder.

Contributors HS and TO designed the study and HS wrote the protocol.

Competing interests None.

Ethics approval Central Review Board of the National Hospital Organization.

Provenance and peer review Not commissioned; externally peer reviewed.

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