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ScienceDirect
European Psychiatry 21 (2006) 548–550
EUROPEAN PSYCHIATRY
http://france.elsevier.com/direct/EURPSY/

Short communication

# Acetylcholinesterase inhibitor donepezil in the treatment of cognitive deficit in schizophrenia. Subanalysis of the active branch from Czech extended double blind study

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Available online 23 June 2006

**Abstract**

The article mentions the conclusions of most evidential works investigating donepezil in the treatment of cognitive deficit in schizophrenia. It focuses on an analysis of a sub-group of 20 patients receiving treatment of the donepezil in an extended Czech double-blind placebo controlled study.


*Keywords:* Schizophrenia; Cognitive deficit; Acetylcholinesterase Inhibitors; AChEi; Donepezil

## 1. Introduction

A range of encouraging case reports and open pilot studies indicate that AChEi could be beneficial for the treatment of cognitive dysfunction in schizophrenia [4]. On the other hand, double-blind trials conducted on this subject matter are inconclusive.

Friedman et al. tested donepezil 5 mg and 10 mg as an adjunctive treatment to risperidone in a group of 36 schizophrenic patients. In this double-blind, placebo controlled trial conducted over the course of 12 weeks no significant changes in the parameters of cognitive functions were found [1]. Tůma et al. conducted an analogically organised trial independent of Friedman. On a group of 28 patients the trial did not demonstrate any difference in the effectiveness of donepezil and a placebo in influencing cognitive deficit in schizophrenia [7]. Tugal et al., in a double-blind, placebo controlled, cross-over trial on 12 schizophrenic patients conducted over a period of 12 weeks found no effect of 5 mg donepezil on cognitive performance [6]. Rish et al. [5] and Nahas et al. used fMRI to measure cortical activity during administration of a verbal fluency test. Nahas et al. reported that in sample of 6 schizophrenic patients the fMRI measured activity of the frontal lobes and gyrus cinguli was higher in the subjects receiving donepezil than in the subjects receiving a placebo [3].

## 2. Subjects and methods

The entry criteria of the trial were a diagnosis of schizophrenia, age of 18-50 years, monotherapy by stable dosage of risperidon within the range of 2-5mg daily and 4 weeks' remission of illness. The exclusion criteria were first episode of schizophrenia, other psychiatric diagnosis, physical illness requiring pharmacotherapy, electro-convulsive therapy within the last 6 months, application of a long-acting antipsychotic drug within the last 3 months, sensory disorder, relapse of schizophrenia, obstructive lung disease, bronchial asthma and the requirement for application of concomitant drugs other than those permitted in the protocol of the trial.

All the included patients were treated with a stable dose of risperidon within the range of 2-5mg daily. Zolpidem and klo-

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0924-9338/$ - see front matter © 2006 Published by Elsevier Masson SAS.
doi:10.1016/j.eurpsy.2006.04.008

nazepam were permitted as concomitant medication. Application of zolpidem for insomnia was permitted up to the amount of 10 mg daily, three days consecutively, a maximum of 14x up to the second examination and 28x up to the end of monitoring (day 112). Application of klonazepam was permitted up to a maximum amount of 2 mg daily, up to a maximum cumulative dose of 28 mg over the course of the first 4 weeks and 70 mg up to the end of monitoring. Application of both of these additional substances was prohibited the evening or morning before a planned examination.

Donepezil was titrated to 10 mg. Up to the 28th day 5 mg was applied in the evening. From the 29th day the dose was increased to 10 mg in the evening.

The subjects in the trial were examined 3x (on day 0, day 84 and day 112). Extrapyramidal side effects were evaluated on a Simpson-Angus scale (Simpson-Angus Rating Scale for Extrapyramidal Side Effect, SA) and a Barnes scale (Barnes Akathisia Rating Scale, BAS). Psychopathology was evaluated on the PANSS scale (Positive and Negative Symptom Scale) and the CGI scale (Clinical Global Impression).

A neuropsychological battery for evaluation of cognitive performance comprised the following tests: Sub-tests Logical memory and Verbal pair association from Weschler's Memory Scale (WMS-III), Category Fluency Test (CFT), Rey-Osterrieth test (Complex Figure Test, CFT), Trail Making Test part A (TMT-A), Stroop's test (Colour Word Test), Tower of Hanoi (TOH), Wisconsin Card Sorting Test (WCST, computerised version) and Numeric Square.

The calculations covered determination of average values, standard deviations, pair t-tests and simple analysis of variation. Relative order of cognitive performance was calculated as an average value of order in all cognitive tests. Following determination of the relative order of cognitive performance and determination of the change of order towards the end of monitoring, the relationship of the order (change of order) to demographic and psychopathological characteristics was tested using multiple linear regressions.

## 3. Results

20 patients received donepezil. Paranoid schizophrenia had been diagnosed in 17 of the patients, undifferentiated schizophrenia had been diagnosed in 2 cases and residual schizophrenia had been diagnosed in 1 patient. The group was composed of 9 women and 11 men with an average age of 32.2 years (SD=10.8), the length of education was on average 11.2 years (SD = 1.7). The average length of illness was 9.1 years (SD = 9.6), the average number of hospitalisations was 3.3 (SD = 2.8), the average dose of risperidon was equal to 3.8 mg (SD = 0.7). Within the group 55% of subjects were smokers, who smoked an average of 13 cigarettes daily (SD = 4.6).

From the beginning of the trial, extrapyramidal side-effects were minimal. The average score on the Simpson-Angus scale reached the value of 2.8 (SD = 2.9) upon the first visit, and at the end of the trial was reduced to 1.25 (SD = 2.5, p=0.01). Only two patients reached an aggregate score of 10, which corresponds with mild extrapyramidal complaints.

Mild akathisia occurred in two patients. The average score on the Barnes scale of post-medication akathisia reached values of 0.35 (SD = 0.67) upon the first examination, 0.25 (SD = 0.55) and 0.3 (SD = 0.66) upon the second and third examination. The differences were not statistically significant.

A significant reduction of the overall PANSS score occurred during the course of monitoring. From 45 (SD = 10.3) upon the initial visit to 41.6 (SD = 11.2, p = 0.01) upon the final visit. This reduction was due primarily to an improvement in the sub-scale of positive symptoms from an initial 9.1 (SD = 1.6) to 8.1 (SD=1.7, p=0.01) and to an improvement in the sub-scale of general psychopathology from an initial 23.4 (SD = 5.3) to 21.1 (SD=5.4, p = 0.01).

In cognitive tests, although patients attained somewhat better results at the end of monitoring than at the beginning, these improvements were not statistically significant. The most robust improvement was recorded in the parameter of the Global reproduction scores of the Logical memory test (LM total, ΔLM total = 7.6, SD = 10.4, Effect size = 0.83, p = 0.055).

The order of performance upon the first examination (day 0) had a significant correlation with age (r = 0.5, SD = 0.11, p = 0.01), with the number of hospitalisations (r = 0.6, SD = 0.39, p = 0.002) and with the length of illness (r = 0.6, SD=0.12, p=0.002). Higher age, greater number of hospitalisations and greater length of illness were associated with a worse rating of the patient within the group, and thus with a relatively worse cognitive performance. In the case of risperidon a negative correlation was recorded (r = -0.4, SD = 1.79, p = 0.04). A higher dosage of risperidon on day 0 was associated with a better rating within the group, thus a relatively better cognitive performance. Patients with a higher dose of risperidon had tendency to score better in the Wisconsin Card Sorting Test, in particular in indicators of Perseverative responses (r = -0.39, SD = 0.008, p = 0.05), Perseverative errors (r = -0.38, SD = 0.01, p=0.05) and Conceptual level (r = 0.4, SD = 0.006, p = 0.05).

Similarly, upon the final examination (day 112), the order of cognitive performance had a significant correlation with age (r = 0.41, SD = 0.12, p = 0.04), the number of hospitalisations (r=0.44, SD = 0.44, p = 0.025), and the length of illness (r = 0.63, SD = 0.11, p = 0.001). There was also a statistically significant correlation between the length of education and the order of cognitive performance (r = -0.49, SD = 0.72, p = 0.01). Patients with longer education attained better results with greater frequency at the end of the trial than patients with a shorter period of education.

Initial cognitive performance correlated significantly with the initial PANSS value (r = 0.38, SD = 0.125, p=0.05). Patients with a higher initial PANSS score had a worse cognitive performance more frequently than patients with a lower PANSS score. This relationship was expressed most strongly for the sub-scale of negative symptoms (r = 0.5, SD = 0.21, p = 0.01). The common occurrence of relatively worse cognitive performance and a high score of negative symptoms re-

mained statistically significant also at the end of monitoring ($r = 0.38$, $SD = 0.22$, $p = 0.05$).

Change of cognitive performance (expressed by change of order within the group) between the initial and final examination did not correlate with the demographic characteristics (age, length of illness, number of hospitalisations, length of education, dosage of risperidon and number of cigarettes smoked). Similarly, no significant relationship was found between the change of order and the initial values on the clinical scales PANS, SA, BAS and CGI.

The question was as to whether certain patients improved in cognitive performance following the addition of donepezil more than others, and whether these patients have any common characteristics which would enable prediction of a therapeutic response to donepezil.

From the active branch the 4 patients who improved the most within the relative order of performance between the 1st and 3rd examinations were selected. Their data was compared with the rest of the group, and in particular with the 4 patients who had deteriorated the most within the relative order of cognitive performance in the final examination. No differences in demographic characteristics or in clinical scales were found between these patients.

## 4. Conclusion

In conclusion it is possible to state that the cognitive performance of the sample of 20 schizophrenic patients correlated negatively with the length of the illness, with the number of hospitalizations, with the age and with the negative symtpoms. Patients with longer education reached more frequently better results at the endpoint then patients with shorter period of education.

No group with common demographic or psychopathological characteristics was identified whose cognitive performance showed an improvement in response to the addition of donepezil.

We consider the significant correlation between the dosage of risperidon and cognitive performance at the beginning of the study to be an interesting finding, which supports the previous evidence of beneficial effect of this drug on cognitive deficit in schizophrenia [2].

The final evaluation of both branches of the Czech double-blind trial shall be the subject of a separate statement, which the authors are preparing for publication.

## Acknowledgments

The paper was supported by Research grant of the Ministry of Health of the Czech Republic NF 6753–3/2001 and by Research project MSM 0021620816.

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