Acta Psychiatr Scand 2001: 104: 469–472
Printed in UK. All rights reserved

ACTA PSYCHIATRICA SCANDINAVICA
ISSN 0001-690X

Case report

Donepezil in schizophrenia — is it helpful? An experimental design case study

MacEwan GW, Ehmann TS, Khanbhai I, Wrixon C. Donepezil in schizophrenia — is it helpful? An experimental design case study. Acta Psychiatr Scand 2001: 104: 469–472. © Munksgaard 2001.

Objective: To assess the clinical and cognitive effects of adding donepezil, a reversible acetylcholinesterase inhibitor, to the risperidone treatment of a high functioning stable out-patient with schizophrenia.
Method: Case study using an experimental ABAB design. Assessments were completed objectively by standardized neuropsychological tests and clinical rating scales and subjectively with visual analogue scales.
Results: Strong improvements attributable to donepezil were found for verbal fluency and the patient's subjective response. No adverse changes were noted in psychiatric symptoms or side effects.
Conclusion: Cholinergic enhancement as an adjunctive treatment in schizophrenia should be explored in larger controlled trials.

G. W. MacEwan[1], T. S. Ehmann[1], I. Khanbhai[1], C. Wrixon[2]

[1]Department of Psychiatry, St Vincent's Hospital, Vancouver, Canada and [2]Department of Psychiatry, St Paul's Hospital, Vancouver, Canada

Key words: donepezil; schizophrenia; research design; cognition

Dr Tom Ehmann, Adult Psychiatry, St Vincent's Hospital, 749 W. 33rd Avenue, Vancouver, BC, Canada, V5Z 2K4

Accepted for publication June 25, 2001

Introduction

The cognitive disturbances associated with schizophrenia now represent important treatment targets. Acetylcholine may mediate the allocation of cortical processing and modulate memory, attention, spatial working memory and the maintenance of cortical arousal to motivating stimuli (1). Cholinergic agonists (i.e. physostigmine) improve or reverse cognitive impairments induced by scopolamine, anoxia, ECT and progressive supranuclear palsy (2). However, psychotic symptoms may be influenced by cholinergic mechanisms. It has been argued that increased dopaminergic activity in the nucleus accumbens leads to decreased GABA, thereby increasing cortical cholinergic activity and eventually resulting in psychosis (3). According to this hypothesis, cholinesterase inhibition could alter attentional processes and produce positive symptoms of psychosis. Fortunately, physostigmine reverses methylphenidate-induced exacerbations of psychosis (4). In normal subjects, physostigmine has been reported to produce negative symptoms (5) and a depression-like state (6).

Cholinergic stimulation has produced beneficial cognitive effects in normals (7) and improved IQ test performance in drug-free bipolar patients (8). Since cortical cholinergic systems are not grossly disturbed in schizophrenia (9), it was hypothesized that patients with schizophrenia might benefit cognitively from the adjunctive use of the anticholinesterase inhibitor donepezil.

Case report

GR is a 36-year-old single male with a diagnosis of schizophrenia-paranoid type (in partial remission). He completed university, worked in sales at an insurance company and became psychotic at age 29. Despite successful treatment with risperidone, he was unable to work for 5 years. At entry into the study he had been stable on 2 mg of risperidone for 3 years. No other medications were employed and he had no other physical or psychiatric disorders. At baseline he displayed mild to moderate emotional and social withdrawal, anxiety, tension and stereotyped thinking. No delusions, hallucinations or conceptual disorganization were present. A reading test estimated his premorbid IQ was about 111.

An ABAB single case design was employed. After informed written consent was obtained, donepezil was administered for 1 week at 5 mg per day and then increased to 10 mg per day for a further 11 weeks. A 6-week washout occurred before donepezil

was restarted for an additional 12 weeks. Assessments of psychiatric symptoms, cognition, side effects and global functioning were made at baseline and the end of each phase. Neither patient nor examiners were blinded. Standardized rating scales were used to assess psychiatric symptoms and side effects. A battery of nine common standardized neuropsychological tests assessed verbal memory, working memory, attention, executive functions and motor performance. The measures included the: North American Adult Reading Test; Continuous Performance Test; Rey Verbal Learning Test; Trailmaking Tests Parts A and B; Controlled Oral Word Association Test; Wisconsin Card Sorting Test; Letter Number Sequencing Test; finger tapping; Ruff 2 and 7 Selective Attention Test; Positive and Negative Syndrome Scale (PANSS); Barnes Akathisia Scale; Calgary Depression Scale; Extrapyramidal Symptom Rating Scale; and Clinical Global Impression Scales. Information regarding all measures can be obtained from TSE. Five visual analogue scales ranging from 0 (very poor) to 85 (very good) assessed the patient's perception of his functioning.

GR reported no beneficial effects until receiving 10 mg for several weeks. He then noticed a marked difference in his ability to read. Since onset he had only been able to read a maximum of 15 minutes, whereas during the donepezil trial he read for hours at a time. This ability disappeared again during the post-donepezil washout period and re-emerged during the second treatment trial. On donepezil, he felt better able to mentally juggle facts and figures and contemplated a return to university. The subjective response ratings (Table 1) show he generally perceived improvements during donepezil phases. The initial worsening of his subjective rating concerning ability to perform chores/tasks was not reversed after discontinuation but his score did improve after donepezil was restarted. No meaningful changes in mood or psychiatric symptoms were found on the PANSS or on a scale that assesses depression in schizophrenia. No abnormal movements or other side-effects were ever noted.

Table 1 showing selected cognition scores demonstrates that, because an ABAB design was used, the initial improvements on some measures probably reflects practice effects. However, the most striking result not attributable to practice is the marked increase in word fluency during each donepezil phase. Although card-sorting performance was consistently good, there appears to be a tendency to greater efficiency when on donepezil. Verbal learning, working memory and attention scores did not follow any particular pattern. GR received a perfect accuracy score on each administration of the Continuous Performance Test, a measure of attention. Finger-tapping speeds were normal for each hand and did not change over any phase. Finally, since the study ended almost a year ago he has remained stable on risperidone and enjoys the same level of functioning he experienced at the end of the trial. He is currently receiving donepezil, as he felt his function was decreased when it was discontinued.

Table 1. Selected cognition scores

	Baseline	Donepezil phase 1	End of washout	Donepezil phase 2
Subjective responses (0–85)				
Concentration	25	67	40	58
Conversation with others	27	53	64	61
Handling finances	70	76	59	67
Thinking clearly	39	54	50	67
Everyday tasks/chores	80	64	55	66
Word fluency (no. of words)	25	34	25	36
Card sorting (standard scores)				
% Perseverative errors	96	104	93	115
% Conceptual level responses	94	95	83	107
Categories — max = 6	6	6	6	6
15-item word list (raw scores)				
Trial 1	04	06	06	04
Trial 5	11	13	14	13
Trial 1–5 total	42	54	54	46
Recall 20 minutes	07	11	11	10
Recognition	12	14	15	15
Trails A (s)	28	22	23	19
Trails B (s)	77	68	56	52
Reaction time (msec)	48	36	38	35

Discussion

We believe this is the first report on the use of a cholinesterase inhibitor in an out-patient with schizophrenia. He reported subjective improvements in concentration and clarity of thought along with improved abilities in reading and performance at work. The neuropsychological finding of improved verbal fluency is especially interesting since clozapine, but not risperidone, has been shown to improve fluency (10). Fluency has been shown to be one of the more reliable predictors of functional outcome (11). Some improvement was also seen on neuropsychological measures associated with executive functioning. A cursory look at the differences from baseline to the end of the first trial suggests erroneously that donepezil generated many positive effects. The use of a reversal design allowed for better recognition of practice effects than a simple pre–post comparison. The possibility that acetylcholine enhancement could produce or exacerbate positive symptoms, negative symptoms

or depression was not found in our patient with schizophrenia just as it was not found in donepezil-treated bipolar disorder patients (12). The present study is obviously limited by its use of only one case and from the fact that neither patient nor examiners were blind to treatment phase. The lack of adverse effects, together with the neuropsychological results, suggests that cholinergic enhancement in schizophrenia merits controlled investigations.

References

1. Sarter M, Bruno J. Cognitive functions of acetylcholine: toward a unifying hypothesis. Brain Res Rev 1997;**23**: 28–46.
2. Kertzman C, Robinson D, Litvan I. Effects of physostigmine on spatial attention in patients with progressive supranuclear palsy. Arch Neurol 1990;**47**:1346–1350.
3. Sarter M, Bruno JP. Cortical acetylcholine, reality distortion, schizophrenia and lewy body dementia: too much or too little cortical acetylcholine? Brain Cogn 1998; **38**:297–316.
4. Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ. Antagonistic effects of physostigmine and methylphenidate in man. Am J Psychiatry 1973;**130**:1370–1376.
5. Tandon R, Greden J, Haskett R. Cholinergic hyperactivity and negative symptoms: behavioral effects of physostigmine in normal controls. Schizophr Res 1993;**9**:19–23.
6. Davis K, Hollister L, Overall J, Johnson A, Train K. Physostigmine: effects on cognition and affect in normal subjects. Psychopharmacology 1976;**51**:23–27.
7. Furey M, Pietrini P, Haxby J, Alexander G, Lee H, Meter JV. Cholinergic stimulation alters performance and task specific regional cerebral blood flow during working memory. Proc Natl Acad Sci USA 1997;**94**:6512–6516.
8. Telford R, Worrall E. Cognitive function in manic depressives: effects of lithium and physostigmine. Br J Psychiatry 1978;**133**:424–428.
9. Friedman J, Temporini H, Davies K. Pharmacologic strategies for augmenting cognitive performance in schizophrenia. Biol Psychiatry 1999;**45**:1–16.
10. Meltzer H, McGurk S. The effects of clozapine, risperidone and olanzapine on cognitive function in schizophrenia. Schizophr Bull 1999;**25**:233–255.
11. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring 'the right stuff'? Schizophr Bull 2000;**26**:119–136.
12. Burt T, Sachs GS, Demopulos C. Donepezil in treatment-resistant bipolar disorder. Biol Psychiatry 1999;**45**:959–964.

Invited comment

Pharmacotherapy of cognitive impairment in schizophrenia: variant approaches

In recognizing the important contribution of cognitive deficits to poor functional outcome in schizophrenia, pharmacological routes to amelioration of such deficits are far less clear. At least three general strategies suggest themselves: i) exploration of new, second-generation antipsychotics for domains of efficacy which extend beyond psychopathology to cognition; ii) importation from a therapeutic area other than schizophrenia of a treatment modality having a favourable, even if modest, effect on cognition; and iii) identification of a novel, radical approach to treatment, ideally deriving from some increase in understanding of the pathobiology of schizophrenia.

The first option holds some, if so far unfulfilled, promise and is currently a major research front (1, 2), while the third option is made difficult by our all-too-restricted understanding of schizophrenia itself (3); hence the second option is logical and constitutes an attractive, interim approach at a practical level. In these terms, this case report is to be welcomed.

While the limitations of the case study of MacEwan and colleagues (4) are readily apparent, their findings from an ABAB design challenge us beyond those limitations. However, although provocative, any relevant enthusiasm must be tempered by uncertainties as to not only the reproducibility, specificity and generality of any such effect to similar patients, but also the extent to which the cognitive deficits of older, more chronically ill patients, or of younger, first-episode patients, might be less, more or not malleable under similar conditions.

Perhaps the greatest role of cases such as this is heuristic. It is reassuring that double-blind, placebo-controlled studies of the effects of donepezil on cognitive impairment in schizophrenia have been ongoing (e.g. (5)) and are now ready to provide more substantive data.

John L. Waddington PhD, DSc
Professor of Neuroscience,
Department of Clinical Pharmacology,
Royal College of Surgeons in Ireland,
St Stephen's Green,
Dublin 2,
Ireland

Acknowledgements

The author's studies are supported by the Stanley Foundation.

References

1. Green MF, Braff DL. Translating the basic and clinical cognitive neuroscience of schizophrenia to drug development and clinical trials of antipsychotic medications. Biol Psychiatry 2001;**49**:374–384.
2. Harvey PD, Keefe RSE. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 2001;**158**:176–184.
3. Waddington JL, Morgan MG. Pathobiology of schizophrenia: implications for clinical management and treat-

ment. In: Lieberman JA, Murray RM, eds. Comprehensive care of schizophrenia. London: Martin Dunitz, 2001:27–35.
4. Macewan GW, Ehmann TS, Khanbhai I, Wrixon C. Donepezil in schizophrenia — is it helpful? An experimental design case study. Acta Psychiatr Scand 2001;**104**:00–00.
5. Friedman JI, Alder DN, Howanitz E, Temporini H, Harvey PD, Davis KL. Effects of donepezil on cognition, symptoms and movement disorders in patients with chronic schizophrenia. Schizophr Res 2001;**49**:228.