Available online at www.sciencedirect.com

SCIENCE DIRECT®

Schizophrenia Research 85 (2006) 73–83

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Cognitive effects of adjunctive 24-weeks Rivastigmine treatment to antipsychotics in schizophrenia: A randomized, placebo-controlled, double-blind investigation

Tonmoy Sharma [a,*], Catherine Reed [b], Ingrid Aasen [b,c], Veena Kumari [b,c]

[a] *Clinical Research, Clinical Neuroscience Research Centre, 7 Twisleton Court, Priory Hill, Dartford, Kent DA1 2EN, UK*
[b] *Psychological Medicine, Institute of Psychiatry, King's College London, London, UK*
[c] *Psychology, Institute of Psychiatry, King's College London, London, UK*

Received 14 February 2006; accepted 3 March 2006

Abstract

Cognitive impairment has the greatest impact on illness outcome in schizophrenia. The most significant challenge in schizophrenia therapeutics, thus, is to develop an efficacious treatment for cognitive impairments. Acetylcholinesterase inhibitors, such as Physostigmine and Rivastigmine, are considered effective treatments for cognitive decline in Alzheimer's Disease, where the loss of cholinergic neurons is thought to be responsible for various cognitive deficits. The current study investigated the cognitive effects of Rivastigmine given as an add-on therapy to antipsychotic-treated schizophrenia patients in a placebo-controlled double-blind design. The study initially involved 40 patients, of which 21 patients (11 assigned to Rivastigmine and 10 assigned to placebo) agreed to continued participation, remained on the study drug, and underwent assessment of executive functioning, verbal skills, verbal and spatial working memory, attention and psychomotor speed on three occasions: (i) at baseline, and then (ii) after 12 weeks and (iii) 24 weeks of treatment with placebo or Rivastigmine. The results failed to reveal significant improvement on any cognitive measure with Rivastigmine treatment, compared with the placebo treatment. Some cognitive variables showed significant practice effects in both the placebo and Rivastigmine groups. No effects were noted in symptoms or side effects ratings. The beneficial cognitive effects of Rivastigmine seen in an open-label preliminary study are not substantiated by this study. Future studies should investigate the effects of other procholinergic drugs, such as Galantamine, which also act on the nicotine receptors and may produce stronger cognitive effects in schizophrenia.

Keywords: Schizophrenia; Cholinergics; Cognitive enhancement; Nicotine

1. Introduction

Cognitive impairment is an enduring feature of schizophrenia (review, Rund, 1998) which is often present at illness onset (Riley et al., 2000) and persists

* Corresponding author. Tel.: +44 1322 286862; fax: +44 1322 286861.
E-mail address: t.sharma@psychmed.org.uk (T. Sharma).

0920-9964/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2006.03.037

regardless of a change in patients' symptom state (Hughes et al., 2003). Following the observation that cognitive impairment is more strongly related to the functional outcome than the severity of positive or negative symptoms (Green, 1996; Velligan et al., 1997; Addington and Addington, 1999; Evans et al., 2003), cognition has become a prime treatment target in schizophrenia (Sharma and Harvey, 2000; Harvey et al., 2004).

The acetylcholinesterase inhibitors (AChE-Is), such as Donepezil, Tacrine, Rivastigmine and galantamine, are known to be effective in treating cognitive decline in Alzheimer's disease (AD; reviews Doody, 2003; Giacobini, 2003; Terry and Buccafusco, 2003; Harry and Zakzanis, 2005). Although schizophrenia is not associated primarily with a cholinergic pathology, the decreases in choline acetyltransferase (ChAT) levels at postmortem have been found to be associated with the severity of antemortem cognitive deficits in patients with schizophrenia (Powchik et al., 1998). These data taken together with other evidence showing cognitive facilitation with cholinergic stimulation in experimental animals (e.g. Mandel et al., 1989; Decker and McGaugh, 1991) suggest that patients with schizophrenia may benefit from procholinergic treatment (Friedman et al., 1999). Cognitive improvement with some atypical antipsychotics, such as Clozapine, has also been hypothesised to involve their ability to increase ACh (Shirazi-Southall et al., 2002). However, cognitive functioning in patients treated with atypical antipsychotics generally remains below normative standards so there is still a need for an alternative treatment (Lehman et al., 1995).

In recent years, several groups have investigated the effects of AChE-Is on cognitive functions in schizophrenia. Preliminary studies and case reports showed significant cognitive improvements with 4–12 weeks Donepezil treatment as add-on therapy in schizophrenia or schizoaffective disorder (Risch et al., 2001; MacEwan et al., 2001; Howard et al., 2002; Stryjer et al., 2002; Buchanan et al., 2003). There is preliminary functional magnetic resonance imaging (fMRI) evidence for its effects at the neural level in schizophrenia (Risch et al., 2001; Nahas et al., 2003). Two 12-weeks randomized, double-blind, placebo-controlled studies, however, failed to observe significant cognitive effects of Donepezil in this population (Friedman et al., 2002; Tugal et al., 2004).

More recently, a preliminary study has reported cognitive improvement with Rivastigmine in schizophrenia (Lenzi et al., 2003; $n=16$ of which 6 discontinued, significant memory and attention improvements evident at 2 and 3 months post-treatment in remaining 10 patients). Rivastigmine is classified as an intermediate-acting or pseudo-reversible agent due to its long inhibition of AChE (up to 10 h), compared to Tacrine and Donepezil which are classified as short-acting or reversible agents (binding to AChE hydrolysed within minutes) (Polinsky, 1998). In AD, it has been found to improve daily activities, cognitive functions and psychopathology, with effects occurring as early as 12 weeks post-treatment (reviews, Birks et al., 2000; Jann, 2000; Williams et al., 2003). We recently reported robust increases in activation in brain regions associated with spatial attention and visual processing but only small (and non-significant) improvements in measures of attention and working memory with 12-weeks adjunctive Rivastigmine treatment to antipsychotics in schizophrenia patients (Aasen et al., 2005; Kumari et al., 2006).

In this report we describe the cognitive effects of 12- and 24-weeks adjunctive Rivastigmine treatment to antipsychotics in stable schizophrenia patients. Given the pharmacological properties of this drug and previously described cognitive effects in AD, we expected to find cognitive improvement with Rivastigmine treatment, especially when assessed at 24-weeks post-treatment, relative to the placebo, in this study. We also examined the effect of Rivastigmine treatment on symptoms given the earlier reports showing a beneficial effect of Donepezil on psychotic symptoms (Stryjer et al., 2003) and depression (Risch et al., 2001) in patients with schizophrenia.

2. Methods

2.1. Subjects

Forty patients with a diagnosis of schizophrenia, diagnosed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995), were recruited from a catchment area including inner and outer London hospital trusts and via referrals from community mental health teams.