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RESEARCH LETTER

Risperidone and rivastigmine and agitated behaviour in severe Alzheimer's disease: a randomised double blind placebo controlled study

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INTRODUCTION

A recent study (Ballard *et al*., 2005) comparing the cholinesterase inhibitor rivastigmine with quetiapine concluded that 'central cholinesterase inhibitors and atypical antipsychotics are not effective for the treatment of agitation in people with dementia'. However, there have been no comparative studies of the most widely prescribed atypical antipsychotic, risperidone with a cholinesterase inhibitor for the treatment of agitation.

METHODS

We compared risperidone and rivastigmine in nursing home patients with severe probable AD (MMSE <6 points; NINCDS-ADRDA criteria (McKhann *et al*., 1984), and clinically significant agitation (Cohen-Mansfield Agitation Inventory (CMAI) score (Cohen-Mansfield, 1995) >39 points for at least 6 weeks) in a randomized double-blind placebo-controlled trial over six-weeks. Patients were excluded if they had a previous exposure to a cholinesterase inhibitor or had ever received psychotropic drugs of greater than 20 mg thioridazine (or its equivalent).

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At baseline patients were randomized to receive either risperidone 0.5 mg o.d. for 2 weeks followed by an increase to risperidone 0.5 mg b.d. for a further 4 weeks or rivastigmine 1.5 mg b.d. for 2 weeks followed by an increase to rivastigmine 3 mg b.d. for a further 4 weeks. Both risperidone and rivastigmine were re-encapsulated and treatment allocation randomized by an independent pharmacist so that both drugs had an identical physical appearance and dosing regimen. All participants and raters were blind to the treatment being offered. Clinical evaluation using the CMAI; the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987); medication compliance checks and adverse event (AE) monitoring took place at screening, baseline and at 2, 4 and 6 weeks.

Ethical approval for the study including the study protocol was granted by the Hampshire and South-West Local Research Ethics Committee (LREC/027/01/t).

RESULTS

Study recruitment was stopped early from a planned 32 patients to 28 patients following the guidance on the use of atypical antipsychotics issued by the committee for the safety of medicines (Committee on the Safety of Medicines, 2004) reducing the power of the study from 80% to 74%. Efficacy analyses were performed on the intent-to-treat (ITT) population.

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Table 1. Baseline (ITT) characteristics and changes in CMAI and UPDRS from baseline to 6 weeks: differences between treatment groups

	Risperidone ($n = 12$)	Rivastigmine ($n = 15$)	p-value
Baseline (ITT) characteristics			
Age Mean (SD) years	85.3 (5.0)	87.0 (6.5)	$p = 0.47$
Females Number (%)	8 (66.7)	12 (80.0)	$p = 0.36$
MMSE Mean (SD) points	6.3 (4.6)	9.0 (5.5)	$p = 0.19$
CMAI Mean (SD) points	69.3 (13.5)	68.0 (14.5)	$p = 0.80$
UPDRS Mean (SD) points	9.1 (5.7)	9.1 (4.6)	$p = 0.98$
Changes from Baseline to 6 weeks			
CMAI change Mean (SD) points	−24.8 (21.4)	−1.9 (13.7)	$p = 0.002$
UPDRS change Mean (SD) points	1.4 (4.8)	−1.8 (5.8)	$p = 0.14$

CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination; UPDRS = Motor section of unified Parkinson's Disease Rating Scale.

A total of 70 patients were screened of whom 28 entered the study. The mean age of the patients entering the study was 86.1 (SD 5.8) years, with the majority (75%) being women. Reasons for screen failure were largely due to CMAI score <40 points; or diagnosis other than probable AD. One patient enrolled into the study withdrew consent prior to reaching randomization leaving 27 patients available for the ITT analysis. Randomization of patients led to two treatment groups who were similar with respect to their demographic characteristics and psychometric test scores (Table 1).

Adverse events were experienced in a total of four (33%) of the 12 subjects who entered the risperidone arm (one chest infection; one persistent agitation with constipation; one transient ischaemic attack and one cellulitis) and nine (60%) of the 15 subjects who entered the rivastigmine arm (three nausea and vomiting; three persistent agitation; one constipation; one chest infection; one skin rash). This adverse event rate was not significant ($\chi^2 = 1.9$, $p > 0.1$) between treatment arms.

Changes in psychometric scores following randomization are shown in Table 1. Comparing changes in CMAI scores at baseline with week six, patients who received risperidone experienced a mean difference (improvement) of −22.9 points compared with the rivastigmine treated group at 6 weeks [95% confidence interval (CI) −36.9 to −8.9; $p = 0.002$]. The risperidone treated group also showed significant improvements in the changes in CMAI scores from baseline at 2 weeks (mean improvement −20.5 points; 95% CI −31.8 to −9.2 points; $p = 0.003$) and 4 weeks (mean improvement −16.1 points; 95% CI −30.7 to −1.5 points). No significant difference were found in treatment emergent extrapyramidal signs as assessed by the UPDRS [mean difference from baseline to 6 weeks 3.2 points; (95% CI −1.1 to −7.5; $p = 0.14$)].

CONCLUSION

This study shows that in the acute treatment of marked agitation in patients with severe AD the atypical neuroleptic risperidone has a greater efficacy than rivastigmine. This study supports the lack of evidence for rivastigmine as an acute treatment for agitation but does not support the generalized statement that atypical antipsychotics are not effective in the treatment of agitation.

DISCLOSURES

Professor C. Holmes and Dr D. Wilkinson have both received honoraria and research donations from Novartis and Shire pharmaceuticals.

This study contains original unpublished work and is not being submitted for publication elsewhere at the same time.

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