J R Coll Physicians Edinb 2016; 46: 101–2
http://dx.doi.org/10.4997/JRCPE.2016.208

Should ReSPonD change falls prevention in Parkinson's disease?

[1]JL Taylor, [2]D Sumukadas
[1]Specialty Registrar, [2]Consultant, Department of Medicine for the Elderly, Ninewells Hospital, Dundee, UK

TITLE Rivastigmine for gait instability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial

AUTHORS Henderon EJ, Lord SR, Brodie MA et al.

JOURNAL *Lancet Neurol* 2016; 15: 249–58. http://dx.doi.org/10.1016/S1474-4422(15)00389-0

DECLARATION OF INTERESTS No conflicts of interests declared

Correspondence to D Sumukadas
Department of Medicine for the Elderly
Ninewells Hospital
Dundee
UK

e-mail d.sumukadas@nhs.net

SUMMARY

The ReSPonD trial was a single-centre, double-blind, placebo controlled phase 2 trial to investigate whether the acetylcholinesterase inhibitor rivastigmine would reduce gait variability in Parkinson's disease (PD).[1] A total of 130 patients with PD were randomised to receive twice daily oral rivastigmine or placebo for 32 weeks in a 1:1 ratio. Rivastigmine was uptitrated to a target dose of 12 mg per day over 12 weeks. Inclusion criteria were: at least one fall in the preceding year, ability to walk 18 metres without a walking aid, no previous exposure to acetylcholinesterase inhibitors and importantly no dementia or other neurological, orthopaedic or visual problem that interfered with gait. The primary endpoint was the difference in step time variability between the two groups at 32 weeks. Step time variability was measured with a triaxial accelerometer during three different variations of an 18 metre walking task: normal walking, a simple dual task (walking while naming words beginning with a single letter) and a complex dual task (walking while naming words alternating between two letters).

At the end of the study period, the treatment arm had a reduction in step time variability of 28% for normal walking (geometric mean 0·72, 95% CI 0·58–0·88; p = 0·002) and 21% in the simple dual task (0·79; 0·62–0·99; p = 0·045). There was a non-significant trend towards improvement for the complex dual task. Adjusted falls incidence rate ratio was considerably lower in the rivastigmine group (0.55, 95% CI 0.38–0.81; p = 0.002). There was a higher incidence of gastrointestinal side effects 52% vs 18% (predominantly nausea) in the rivastigmine group.

The authors concluded that rivastigmine can improve gait stability and might reduce falls in patients with PD, necessitating a phase 3 randomised controlled trial with falls as the primary outcome.

OPINION

Rivastigmine is a licensed treatment for PD dementia, so clinical application in this patient group is already established.[2,3] The aetiology of falls in PD is multifactorial. Current approaches to falls prevention in PD with exercise-based interventions have had conflicting outcomes when studied in clinical trials, with some evidence supporting Tai Chi.[4,5] Given the frequency of and morbidity associated with falls in PD, a pharmacological approach to falls prevention is an attractive prospect. Although dopaminergic depletion is the primary deficit and there is some evidence for improvement in gait variability with levodopa use,[6] falls remain common. Cholinergic impairment in PD may be implicated in not only cognitive impairment but also in gait disturbance,[7] suggesting a potential role for acetylcholinesterase inhibitors in falls reduction.

So does ReSPonD herald a new era for falls prevention in Parkinson's disease?

Looking more closely at the data there are some important considerations. At baseline there were some important differences between the groups, with more women and lower daily levodopa dose in the treatment arm. Intra-individual factors are important in gait variability and the authors have adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls which could mitigate the differences.[8] The primary outcome of reduction in step time variability included three measures and testing for a number of secondary outcomes was conducted. This included rate of falls per month, gait speed, fall risk (Physiological Profile Assessment falls risk score), fear of falling (short-form Iconographical Falls Efficacy Scale); controlled leaning balance; episodes of freezing gait in the past month; cognition and mood (Montreal Cognitive Assessment, Frontal Assessment Battery, Geriatric

Depression Scale and Cognitive Failures Questionnaire total score); disease severity (MDS-UPDRS); levodopa dose changes and quality of life (EuroQoL EQ5D-5L). Multiple statistical testing was performed with no formal correction, which may have increased the likelihood of false positive associations. Analyses were conducted on study completers only, with higher (albeit non-significant) attrition in the treatment arm (dropout of ten patients vs six in the placebo arm), which would tend to magnify any beneficial treatment effect. Consistent with this, a sensitivity analysis using imputation for missing data showed treatment benefit only in the normal walk task.

Application of these study findings in clinical practice is limited by the strict inclusion and exclusion criteria, in particular the exclusion of those requiring walking aids. Likewise, given the high prevalence of dementia and multimorbidity in PD patients, exclusion of patients with dementia or other neurological, visual or orthopaedic problems interfering with gait limits generalisability and clinical applicability. There is currently no recommended treatment for mild neuropsychiatric symptoms that is well tolerated by PD patients. This study could sway the clinician towards commencing rivastigmine in patients with mild neuropsychiatric and mild cognitive impairment. However one should keep in mind that weight loss is an important problem for many PD patients, and with almost half of the rivastigmine group suffering gastrointestinal disturbance, this side effect could exacerbate weight loss. Dizziness was more common in the rivastigmine group; other trials of medications for dementia report more syncope in the treatment arms.[9] While recent studies of acetylcholinesterase inhibitors in Alzheimer's disease also support an improvement in gait variability,[10] a systematic review of studies using acetylcholinesterase therapy in PD patients showed no improvement in falls risk.[11]

So should we start using rivastigmine to prevent falls in patients with PD? This study certainly heralds an interesting prospect for future large randomised controlled trials looking directly at falls rate and risk. However, the neutral systematic review results and tight inclusion criteria of the current trial suggest that larger studies that better reflect patients found in the average Parkinson's clinic are probably needed before clinical practice changes.

REFERENCES

1 Henderson EJ, Lord SR, Brodie MA et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* Neurol 2016; 15: 249–58. http://dx.doi.org/10.1016/S1474-4422(15)00389-0

2 Emre M, Aarsland D, Albanese A et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004; 351: 2509–18.

3 Joint Formulary Committee. *British National Formulary.* 71st ed. London: BMJ Group and Pharmaceutical Press; 2016.

4 Canning CG, Sherrington C, Lord SR et al. Exercise for falls prevention in Parkinson disease: A randomized controlled trial. *Neurology* 2015; 84: 304–12. http://dx.doi.org/10.1212/WNL.0000000000001155

5 Li F, Harmer P, Fitzgerald K et al. Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med* 2012; 366: 511–9. http://dx.doi.org/10.1056/NEJMoa1107911

6 Schaafsma JD, Giladi N, Balash Y et al. Gait dynamics in Parkinson's disease: Relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci* 2003; 212: 47–53.

7 Rochester L, Yarnall AJ, Baker MR et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain* 2012; 135: 2779–88. http://dx.doi.org/10.1093/brain/aws207

8 Senden R, Meijer K, Heyligers IC et al. Importance of correcting for individual differences in the clinical diagnosis of gait disorders. *Physiotherapy* 2012; 98: 320–4. http://dx.doi.org/10.1016/j.physio.2011.06.002

9 Kim DH, Brown RT, Ding EL et al. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. *J Am Geriatr Soc* 2011; 59: 1019–31. http://dx.doi.org/10.1111/j.1532-5415.2011.03450.x

10 Montero-Odasso M, Muir-Hunter SW, Oteng-Amoako A et al. Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. *J Alzheimers Dis* 2015; 43: 193–9. http://dx.doi.org/10.3233/JAD-140759

11 Pagano G, Rengo G, Pasqualetti G et al. Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2015; 86: 767–73. http://dx.doi.org/10.1136/jnnp-2014-308764