INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2004; **19**: 641–644.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1138

Delirium in elderly hospitalised patients: protective effects of chronic rivastigmine usage

Paul L. J. Dautzenberg[1]*, Leonie J. Mulder[1], Marcel G. M. Olde Rikkert[2], Cees J. Wouters[1] and Anton J. M. Loonen[3]

[1]*Department Geriatrics Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, The Netherlands*
[2]*Department of Geriatrics, University Medical Centre Nijmegen, The Netherlands*
[3]*Department of Clinical Pharmacology, DeltaBouman Psychiatric Hospital, Poortugaal, The Netherlands*

SUMMARY

Objectives To investigate the efficacy of the chronic usage of the cholinesterase inhibitor rivastigmine in patients with dementia in the prevention of delirium in case of hospitalisation.
Design Retrospective cohort study.
Setting Non-geriatric wards of an 1120 bed general teaching hospital in 's-Hertogenbosch, The Netherlands.
Participants Of a group of 366 hospitalised patients, treated by the geriatric consultation team from January 2002 until June 2003, the patients who used rivastigmine chronically were compared with a randomly selected subgroup of all patients not treated with rivastigmine.
Measurements The occurrence and duration of a delirium, co-morbidity, use of medication, length of hospitalisation and psychosocial data were collected from the medical charts of the geriatric consultation team.
Results 11 patients (3%) were chronic rivastigmine users. A control group of 29 subjects was randomly selected from the non-rivastigmine users of the patient population. In the group that used rivastigmine five patients (45.5%) developed a delirium, compared with 8 (88.9%) in the control group ($p < 0.05$).
Conclusions Chronic rivastigmine use may contribute to the prevention of a delirium in a high-risk group of elderly hospitalised patients suffering from dementia. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — delirium; prevention; rivastigmine; high-risk

INTRODUCTION

Delirium is common among elderly patients with dementia. In a review of 14 articles, Fick and colleagues stated that in a community population with dementia and in hospitalised patients with dementia the prevalence of delirium ranged from 7–25% and from 32–86%, respectively (Fick *et al*., 2002). Previous studies have documented the poor long-term outcome of delirium, as reflected by an increased rate of functional and cognitive decline, rehospitalisation, nursing home placement, and death (Francis 1992; Liptzin and Levkofs, 1992; Inouye *et al*., 1998).

Our knowledge of the pathophysiology of delirium is rather fragmentary (Van der Mast, 1998; Flacker and Lipsitz, 1999). The main neurochemical correlate of delirium is a decreased cholinergic activity. Known anticholinergic drugs can precipitate delirium (Tune, 2000). Exposure of anticholinergic medications was independently and specifically associated with a subsequent increase in the severity of delirium in elderly patients with diagnosed delirium (Han *et al*., 2001). In case-reports, cholinergic drugs can improve (Wengel *et al*., 1998), reverse (Fischer, 2001, Dautzenberg *et al*., 2004) and prevent (Dautzenberg *et al*., 2003) delirium.

The age-related loss of cholinergic reserve and the focal loss of cholinergic cell bodies in the nucleus basalis of Meynert (Francis *et al*., 1999) may be why delirium is more common in older individuals and in patients with dementia. Patients with Alzheimer's

*Correspondence to: Dr P. L. J. Dautzenberg, Department Geriatrics Jeroen Bosch Ziekenhuis, Deutersestraat 2, 5223 GV' s-Hertogenbosch, The Netherlands. E-mail: p.dautzenberg@jbz.nl

Received 8 December 2003
Accepted 1 March 2004

disease and Lewy Body Dementia are treated with cholinesterase inhibitors. Until December 2003, rivastigmine was the only cholinesterase inhibitor available in The Netherlands. Until now, it is not clear, if the chronic use of rivastigmine can prevent a delirium.

The purpose of this study, using retrospectively data from hospitalised patients on non-geriatric wards of a teaching hospital, who were treated by the geriatric consultation team (GCT), was to examine the relationship between the chronic usage of rivastigmine and the occurrence of delirium, while taking other known risk factors into account.

METHODS

Patients

The GCT treated four hundred and forty-two patients on non-geriatric wards in the period January 2002–June 2003. The study population was a cohort of 366 of these patients, who were treated because of the appearance of a delirium or who were considered to be at high-risk of develop delirium by their treating physician.

Procedures

The GCT (consisting of a geriatric specialist nurse, a geriatric resident and a geriatric consultant) treats patients on the request of the primary responsible physician on non-geriatric wards. During the study period, 40 000 admissions occurred in the hospital in study. Of the older people of these admissions, 2–5% are referred to the GTC, because of behavioural disturbances, cognitive decline, depression and delirium. Routine daily contact with patients and the GCT is performed from Monday until Friday. The mean weekly time spent in consultation by the nurse, resident and consultant is respectively 30, 12 and 4 hours. On all wards of the hospital, a protocol regarding delirium is known. According to this protocol, the normal clinical team offers non-pharmacological supportive environmental measures for high-risk patients on a routine basis and if necessarily, the primary responsible physician sometimes starts a low dosage of haloperidol. In case of non-responding to this routine measures, the GTC coordinates and initiates the pharmacological treatment of a delirium.

To make sure that all the patients with chronic rivastigmine use were included, the charts of the GCT were checked for omissions using the hospital pharmacy's list of patients that used rivastigmine on any moment during admission. After this procedure, the patients were divided into group R (chronic rivastigmine user) and a control group N that was randomly selected from all patients seen by the GCT, who did not use rivastigmine during admission.

In case of a diagnosed delirium during the time of hospitalisation of the patient, based on DSM-IV criteria, this was routinely recorded on the medical charts of the GCT. No effort was made to assess the subtypes of delirium. Due to the retrospective character, for this study, the end of the delirium was determined as the start of a period of 2 consecutive nights without a sleep disorder probably due to delirium.

The following predisposing and precipitating factors for a delirium were registered: age, sex, marital state, reason for admission, the number of drugs used, and the presence of pre-existing residential care, pre-existing dementia, Parkinsonism, surgical intervention, dehydration and infection (4 days before treatment of GCT until 4 days after start treatment: BSE $>$ 30 mm/h, CRP $>$ 20 mg/l, white cell count $> 10^9$. Also, the length of hospitalisation and patient's outcome were recorded.

Statistical analysis

Using the unpaired *t*-test, differences between incidence rates of delirium in rivastigmine users and controls and between means of patient- and delirium characteristics were tested by comparing 95% confidence intervals (CIs). All variables were tested for normality.

RESULTS

In total 366 patients were seen by the GCT in the study period related to the problem of delirium. Data for two of these cases were incomplete. Eleven patients (3%) were chronic rivastigmine users (group R). In 21 patients, the GCT started rivastigmine, because of chronic delirium (>14 days). Of the remaining 332 patients, 30 patients were randomly selected (Group N). In Group N, one patient was readmitted to the hospital. For this study, the data of the longest hospital stay of this patient were included. So, 29 subjects formed group N. The mean duration of treatment by the GCT was longer in Group R compared to Group N ($p = 0.04$).

The medical and psychosocial characteristics of the patients of group R and N and their predisposing and precipitating factors for a delirium are presented in Table 1. The two groups are not identical. Compared to group N, more patients in group R were demented before admission, but this was directly linked to the selection criterion.

Table 1. The psychosocial characteristics of the patients and predisposing and precipitating factors for a delirium in group R (chronic users of rivastigmine) and group N (non-chronic users of rivastigmine). (95% Conficence intervals)

	Group R ($n=11$)	Group N ($n=29$)
Mean age years	79.4 (65.4–93.4)	78.7 (61.1–96.3)
Female (%)	81.8 (59.0–104.6)	51.9 (33.0–70.8)
Married (%)	45.5 (16.1–74.9)	33.3 (15.5–51.0)
Pre-existent		
Non-residential care (%)	90.9 (73.9–100)	81.5 (66.8–96.2)
Dementia (%) #	100	59.3 (40.8–77.8)
Parkinsonism (%)	36.4 (8.0–64.8)	3.7 (−3.4–10.8)
Surgery (%)	54.5 (25.1–83.9)	55.6 (36.9–74.3)
Hip fracture (%)	63.6 (35.2–92.0)	22.2 (6.5–37.9)
Dehydration (%)	27.3 (1.0–53.6)	48.1 (29.2–67.0)
Infection (%)	45.5 (16.1–74.9)	44.4 (25.7–63.1)
Mean number of drugs	7.9 (0.5–15.3)	9.0 (−1–19.0)

significant result ($p<0.05$).

Table 2. Incidence and the outcome of delirium in group R (chronic rivastigmine use) and group N (non-chronic use of rivastigmine) (95% Conficence intervals)

All CIs	Group R ($n=11$)	Group N ($n=29$)
Incidence delirium (%) #	45.5% (16.1–74.9)	88.9 (77.1–100.7)
Reverse delirium (%)	100	91.7 (81.3–102.1)
Mortality (%)	0	0
Mean treatment GCT days#	21.4 (−2.2–45.0)	12.2 (−10.8–35.2)
Mean length of stay hospital days	40.6 (−20–101.2)	28.4 (−16.8–73.6)
At discharge		
Non-residential care (%)	54.5 (25.1–83.9)	55.6 (36.9–74.3)

significant result ($p<0.05$).

Table 3. The characteristics of the patients in group R, divided in delirious and non-delirious. Because of the small groups, no efforts were made to investigate significant differences

	Non-delirious ($n=6$)	Delirious ($n=5$)
Mean age years	79.2	81.4
Female (%)	67	100
Married (%)	50	40
Pre-existent		
*Non-residential care (%)	83	100
*Indication rivastigmine		
Alzheimer' Disease (%)	67	60
Lewy Body Dementia (%)	33	40
Surgery (%)	67	40
Hip fracture (%)	83	60
Dehydration (%)	17	0
Infection (%)	17	40
Mean number of drugs	8.2	7.8

The incidence and the outcome of the delirium is presented in Table 2. Compared to group N, less patients in group R had a delirium (respectively 88.9% (CI 77.1–100.7) versus 45.5% (CI 16.1–74.9). Mortality was remarkably low in both groups.

The characteristics of the patients in group R, divided in delirious and non-delirious are presented in Table 3. Because of the small groups, no efforts were made to investigate significant differences. A delirium occurred in both indications for chronic rivastigmine use, e.g. in patients with Alzheimer' disease and well in patients with Lewy Body Dementia.

DISCUSSION

Old hospitalised patients with a high frequency of dementia, hip fractures, infection, Parkinsonism and polypharmacy form this study population. In this study population, the incidence of a delirium was significantly lower in the group of patients with chronic use of rivastigmine, compared to the control group (45.5% vs 89.9%), although in group R there were even more patients with dementia, a well known risk factor for delirium (Fick *et al*., 2002). The occurrence of a delirium seems not to be influenced by the indication for chronic rivastigmine use.

Drug treatment of delirium requires careful consideration of the balance between the effective management of symptoms and potential adverse effects. Antipsychotic drugs are the most commonly used drugs (Meagher, 2001; Brown and Boyle, 2002). However, there is a need for an alternative treatment. First, adverse effects due to haloperidol are common in elderly patients and this is even the case at low dosages. Atypical antipsychotic drugs have been used successfully in uncontrolled case series (Sipahimalani *et al*., 1997; Sipahimalani and Massard, 1998). However, although certain adverse effects may be less common for these atypical antipsychotic drugs, there are no data available that support their routine use in delirium, as their advantages remain unestablished (Brown and Boyle, 2002). Secondly, drugs such as antipsychotics and benzodiazepines can worsen the delirium and can exacerbate underlying causes (Brown and Boyle, 2002). Finally, as many patients with delirium still have residual symptoms at the time of discharge from hospital (Meagher, 2001; Brown and Boyle, 2002, Kiely *et al*., 2003), there may be a need for prolonged drug treatment for weeks or months while living in community, even after treating the direct cause of the delirium. Chronic usage of antipsychotic drugs is associated with a high risk of adverse events, such as falls, whereas chronic use

of other drugs, e.g. cholinesterase inhibitors (in dementia), is relatively well tolerated.

The current study has some methodological limitations: its retrospective design, the clearly small numbers of patients in the analysed groups, the lack of a clear scoring instrument for the assessment of delirium, the absence of information on the subtypes of delirium, the lack of detailed data on the supportive antipsychotic treatment, the used not extensively elaborated but practice oriented definition for the end of the delirium and the uncertain roll of the treatment of the potential underlying cause of the delirium, e.g. the postoperative pain treatment. Also, there is a change of selection bias. The chronic use of rivastigmine may be a result of a better dementia care regime than that experienced by people with dementia who are not prescribed rivastigmine. The latter, poorer care may mean that physical risk factors and precipitants of delirium are also less well managed. However, in our practice, almost all patients with dementia are referred to the memory clinic of our hospital. Also, rivastigmine may be specifically not prescribed in people with dementia with many or severe co-morbid physical conditions which may themselves increase the risk of delirium. However, the GTC contact period for the non-rivastigmine users was shorter, suggesting less geriatric problems during hospital stay in the non-rivastigmine users. In contrast with this, due to a greater alert for risk for delirium in patients already using rivastigmine by the normal clinical team, the GTC may be contacted long before the start of a delirium.

Despite these difficulties, our results indicate that chronic rivastigmine use may have a preventive effect on the development of a delirium during hospital admission. Prospective randomised controlled trials to evaluate the efficacy of cholinesterase inhibitors in the prevention of a delirium are urgently needed, because of the potential serious consequences of a delirium and its high prevalence and incidence in hospital.

REFERENCES

Brown TM, Boyle MF. 2002. ABC of psychological medicine. Delirium. *BMJ* **325**: 644–647.

Dautzenberg PLJ, Wouters CJ, Oudejans I, *et al*. 2003. Rivastigmine in prevention of delirium in a 65-years old man with Parkinson's disease. *Int J Geriatr Psychiatry* **18**: 555–558.

Dautzenberg PLJ, Mulder LJ, Olde Rikkert MGM, *et al*. 2004. Adding rivastigmine to antipsychotics in the treatment of a chronic delirium. *Age Ageing*. in Press.

Fick DM, Agostini JV, Inouye SK. 2002. Delirium superimposed on dementia: a systematic review. *J Am Geriatri Soc* **50**: 1723–1732.

Fischer P. 2001. Successful treatment of nonanticholinergic delirium with a cholinesterase inhibitor. *J Clin Psychopharmacol* **21**: 118.

Flacker JM, Lipsitz LA. 1999. Neural mechanisms of delirium: current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci* **54**: 239–246.

Francis J, Kapoor WN. 1992. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc* **40**: 601–606.

Francis PT, Palmer AM, Snape M, Wilcock GK. 1999. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry* **66**: 137–147.

Han L, McCusker J, Cole M, *et al*. 2001. Use of medications with anticholinergic effects predicts clinical severity of delirium symptoms in older medical patients. *Arch Intern Med* **161**: 1099–1105.

Inouye SK, Rushing JT, Foreman MD, *et al.* 1998. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med* **13**: 234–242.

Kiely DK, Bergmann A, Murphy KM, *et al*. 2003. Delirium among newly admitted postacute facility patients: prevalence, symptoms and severity. *J Gerontology* **58A**: M441–M445.

Liptzin B, Levkoff SE. 1992. An empirical study of delirim. *Br J Psychiatry* **152**: 334–340.

van der Mast RC. 1998. Pathophysiology of delirium. *J Geriatr Psychiatr Neurol* **11**: 138–145.

Meagher DJ. 2001. Delirium: optimising management. *BMJ* **322**: 144–149.

Sipahimalani A, Sime R, Masand P. 1997. Treatment of delirium with risperidone. *Int J Geriatr Psychopharmacol* **1**: 24–26.

Sipahimalani A, Massand P. 1998. Olanzapine in the treatment of delirium. *Psychosomatics* **39**: 422–430.

Tune E. 2000. Serum anticholinergic activity levels and delirium in the elderly. *Seminars in Clinical Neuropsychiatry* **5**: 149–153.

Wengel SP, Roccaforte WH, Burke WJ. 1998. Donepezil improves symptoms of delirium in dementia: implications for future research. *J Geriatr Psychiatry Neurol* **11**: 159–161.

