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Discontinuation of rivastigmine in routine clinical practice

Suzanne V. Frankfort[1,2]*, Bregje A. Appels[3], Anthonius de Boer[4], Linda R. Tulner[1], Jos. P. C. M. van Campen[1], Cornelis H. W. Koks[2] and Jos H. Beijnen[2,5]

[1]*Department of Geriatric Medicine, Slotervaart Hospital, Amsterdam, The Netherlands*
[2]*Department of Pharmacy & Pharmacology, Slotervaart Hospital, Amsterdam, The Netherlands*
[3]*Department of Medical Psychology, Slotervaart Hospital, Amsterdam, The Netherlands*
[4]*Department of Pharmacotherapy and Pharmacoepidemiology, Faculty of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.*
[5]*Department of Biomedical Analysis, Division of Drug Toxicology, Faculty of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*

SUMMARY

Background Rivastigmine is used for symptomatic treatment of mild-to-moderately severe Alzheimer's Dementia (AD). We investigated the frequeny of and reasons for rivastigmine discontinuation in clinical practice and possible predictive factors for discontinuation within the first six months after starting therapy.
Methods A retrospective cohort study was performed in rivastigmine users, who started therapy in a naturalistic setting. A nurse supported a part of the studied cohort, as this was introduced during the study period. Reasons for discontinuation were investigated, including therapy discontinuation if the Maximum Achieved Dose (MAD) was below 6 mg daily. Predictors of discontinuation within the first half year were investigated by logistic regression analysis.
Results Baseline Mini-Mental-State-Examination (MMSE) of included patients ($n = 154$) was 20.1, mean age was 78.4 years and 70% was female. Within 6 months, 61 users (39.6%) discontinued therapy, primarily (59.0%) for adverse events. Thereafter, the main reason for discontinuation was non-response according to clinimetrics. A MAD during the titration phase of 1.5–4.5 mg/day and absence of nurse support are significantly related to discontinuation within 6 months.
Conclusions Rivastigmine is primarily discontinued within the first six months for intolerable adverse events and thereafter mainly for ongoing deterioration. A MAD of 1.5–4.5 mg/day and the absence of nurse support are independently related to discontinuation of rivastigmine within the initial 6 months. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — rivastigmine; discontinuation; clinical practice; adverse events; nurse support

INTRODUCTION

Rivastigmine (Exelon®), an acetylcholinesterase inhibitor, has shown efficacy in the symptomatic treatment of mild to moderately severe Alzheimer's dementia (AD) (Corey-Bloom *et al.*, 1998; Rösler *et al.*, 1999). Known major occurring adverse events of rivastigmine include nausea, vomiting and diarrhoea, whereas bradycardia, dizziness, muscle cramps and weakness are of minor occurrence (Gauthier, 2001).

These adverse events are in certain cases reason for discontinuation of rivastigmine, whereas in others it is not continued because of ongoing decline in cognition.

Geriatricians started prescribing rivastigmine in 1998 in our hospital and since April 2001 it is the policy at the geriatric department that these patients are supported by a nurse. Support consists of intensive telephone contact during the titration phase and regular telephone contact thereafter.

This study aims describing reasons for discontinuation of rivastigmine in routine clinical practice and

*Correspondence to: S. V. Frankfort, Department of Geriatric Medicine, Slotervaart Hospital, Louwesweg 6, 1066 EC Amsterdam, The Netherlands. Tel: +31-20-5124737.
Fax: +31-20-5124753. E-mail: apsfr@slz.nl

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investigating predictive variables of discontinuation within the first half year after starting rivastigmine.

PATIENTS AND METHODS

Patients

This study was carried out in patients with mild-to-moderate severe AD, diagnosed according to the NINCDS-ADRDA criteria (McKahnn *et al.*, 1984), using rivastigmine via the geriatric outpatient department of a general hospital in The Netherlands. Only patients who had responsible relatives or friends who could monitor drug intake were included. Patients were excluded if their data were incomplete. Included patients were followed between May 1998 and September 2004.

Dose titration

Patients started rivastigmine at 1.5 mg twice daily. If tolerated for minimal 2 weeks doses were increased to 3.0 mg twice daily (until the end of 2001) or to once daily 3.0 mg and once daily 1.5 mg (after 2001). If tolerated for another 2 weeks, then doses were titrated to 4.5 mg twice daily (until the end of 2001) or to 3.0 mg twice daily (after 2001). Patients were further titrated by dose increments of 3.0 mg (until the end of 2001) or by 1.5 mg (after 2001), after tolerating therapy for an interval of 2 weeks at each subsequent dose level, to the individual Maximum Achieved Dose (MAD), up to a maximum of 6 mg twice daily. Rivastigmine was discontinued if daily doses of 6 mg were not achieved in case of adverse events, because lower doses are considered to be associated with less efficacy in retaining cognition, performance and behaviour (Corey-Bloom *et al.*, 1998; Rösler *et al.*, 1999).

Neuropsychological assessment

At baseline and at 6-months intervals effectiveness was measured in three domains: cognition, performance in daily living activities and behaviour. Decline or improvement was investigated compared to the previous 6-monthly visit. Rivastigmine had to be discontinued if one of the domains showed major deterioration or if minor decline in two domains without improvement in the third domain was shown. Discontinuation criteria are based upon score differences in a historical control cohort of AD patients. This cohort did not use cholinesterase inhibitors and was tested after an interval of 6 months with the same scales as used in our cohort.

Design and statistical analysis

A retrospective analysis, describing reasons for and time window of discontinuation was carried out. If patients discontinued therapy because of adverse events, the MAD of rivastigmine was also considered and in these patients multiple reasons for discontinuation were counted. The Pearson Chi-square test for categorical data and independent sample *t*-tests for continuous data were used to compare patient characteristics who discontinued rivastigmine use within the first six months and who did not.

Logistic regression analysis was performed to investigate possible risk factors for discontinuation within the first half year after starting therapy. Age was dichotomised to the mean of the population, ≤ 78.4 *vs* > 78.4, number of concomitant drugs to none *vs* ≥ 1, as we hypothesised taking other medication could enhance compliance, baseline MMSE score to ≤ 23 *vs* > 23, MAD of rivastigmine to $<$ twice daily 3 mg *vs* $\geq$ twice daily 3 mg, level of education to low, level 1 through 4, *vs* high, level 5 through 7 as we used a seven-point scale, ranging from less than 6 years of elementary school (score 1) to a university degree (score 7) (Verhage, 1964), and titration schedule as 1.5 mg *vs* 3.0 mg dose increments, because both titration schedules were used during the study period. Gender, involvement of nurse support and place of living were examined as dichotomous variables. When multiple significant ($p < 0.1$) covariates were identified univariately, multivariate logistic analysis was performed.

Statistical calculations were performed with SPSS for Windows (version 11.0, SPSS Inc., Chicago, IL, USA). A *p*-value of 0.05 or less was considered statistically significant.

RESULTS

Patient characteristics

Two patients were excluded because their medical records were incomplete. The 154 included rivastigmine users lived primarily at home, had a mean age of 78.4 years, a mean baseline MMSE score of 20.1 and used a mean daily rivastigmine dose of 7.7 mg (Table 1).

Discontinuation during follow-up

Within the first 6 months 61 users (39.6% of total users) discontinued therapy, primarily for adverse events ($n = 36$, 59.0%) and in 23 patients these adverse events resulted in not achieving a MAD of 6 mg daily. Between 6 and 12 months, 17 users

Table 1. Baseline characteristics

Baseline characteristics	Total population	Within the first half year		*p*-value
		Continued[a]	Discontinued[a]	
	$n = 154$ (100%)	$n = 85$ (55.2%)	$n = 61$ (39.6%)	
Age (years), mean ± SD (range)	78.4 ± 5.8 (56–89)	78.1 ± 6.0 (56–89)	78.8 ± 5.6 (66–89)	0.479
Education				
Level 1–4 (%)/Level 5–7 (%)	110 (71.4)/44 (28.6)	55 (64.7)/30 (35.3)	49 (80.3)/12 (19.7)	0.040
Gender				
Male (%)/Female (%)	45 (29.2)/109 (70.8)	28 (32.9)/57 (67.1)	15 (24.6)/46 (75.4)	0.275
MMSE, mean ± SD (range)	20.1 ± 4.2 (8–28)	20.5 ± 4.3 (8–28)	19.7 ± 4.0 (10–28)	0.258
MAD,[b] mean ± SD (range)	7.7 ± 3.1 (3.0–12.0)	9.2 ± 2.7 (3.0–12.0)	5.8 ± 2.5 (3.0–12.0)	< 0.001
No. of drugs,[c] mean ± SD (range)	2.3 ± 2.0 (0–9)	2.4 ± 2.0 (0–9)	2.1 ± 2.1 (0–8)	0.422
Nurse support				
Yes (%)/No (%)	85 (55.2)/69 (44.8)	54 (63.5)/31 (36.5)	26 (42.6)/35 (57.4)	0.012
Patients place of living				
At home (%)/ Other[d] (%)	140 (90.9)/14 (9.1)	77 (90.6)/8 (9.4)	57 (93.4)/4 (6.6)	0.536
Titration Scheme: Increases				
Increments: 1.5 mg (%)/ Increments: 3.0 mg (%)	86 (55.8)/68 (44.2)	48 (56.5)/37 (43.5)	34 (55.7)/27 (44.3)	0.930

[a] $n = 8$ (5.2%): unknown if patients discontinued therapy.
[b] MAD = Maximum Achieved Dose.
[c] In addition to rivastigmine
[d] e.g. nursing home.

Table 2. Discontinuation during follow-up

Number of patients	<6 months	6–12 months	12–18 months	18–24 months	24–30 months	30–36 months	36–42 months	42–48 months
At start interval	154	85	52	34	18	7	3	3
Still using rivastigmine		11	5	1	3	2	—	1
Lost to follow-up								
Died	3	1	1	—	—	—	—	—
Loss of contact	5	4	1	1	—	—	—	—
Discontinued during interval[a]	61 (39.6)	17 (20.0)	11 (21.2)	14 (41.2)	8 (44.4)	2 (28.5)	—	2 (66.7)
Decline								
Noted by caregivers[b]	10 (16.4)	2 (11.8)	—	1 (7.1)	—	—	—	1 (50.0)
Cognitive test results[b]	—	7 (41.2)	9 (81.8)	6 (42.9)	5 (62.5)	1 (50.0)	—	—
Adverse events[b]	36[c](59.0)	7 (41.2)	1 (9.1)	3[c](21.4)	1 (12.5)	—	—	—
MAD < 6 mg daily[b]	23 (37.1)	1 (5.9)	3 (27.3)	—	—	—	—	—
Not compliant[b]	7 (11.5)	—	—	—	—	—	—	—
Unknown[b]	—	1 (5.9)	—	—	1 (12.5)	—	—	—
Other[b]	8 (11.6)	—	1 (9.1)	4 (28.6)	1 (12.5)	1 (50.0)	—	1 (50.0)

[a] Number (% of total users at start interval).
[b] Number (% of total discontinued users during interval).
[c] Includes 1 bradycardia.

(20.0%) discontinued therapy. Seven patients (41.2%) discontinued for adverse events and nine (52.9%) because of non-response. Between 12 and 18 months, 11 patients (21.2%) discontinued therapy, primarily because of significant decline in test results ($n = 9$, 81.8%). Other reasons for discontinuation ($n = 16$) included refusing to take rivastigmine, malignancies and transfer to a nursing home, where rivastigmine is frequently discontinued, because of financial limitations (Table 2).

Up to 24 months, users were lost to follow-up because of death ($n = 5$) and loss of contact

Table 3. Factors examined in univariate and multivariate logistic regression

Independent variable	Univariate			Multivariate*		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age < 78.5 years	0.76	0.39–1.48	0.418			
Baseline MMSE score < 24	1.70	0.78–3.73	0.185			
Education level 1–4	2.22	1.03–4.82	0.042	2.21	0.90–5.39	0.082
Living at home	1.48	0.43–5.16	0.538			
Male gender	0.66	0.32–1.39	0.276			
MAD 1.5–4.5 mg/day	12.26	3.96–37.92	< 0.001	11.6	3.65–37.0	< 0.001
No co-medication	1.67	0.78–3.60	0.187			
No nurse support	2.35	1.20–4.60	0.013	2.22	1.05–4.73	0.038
Titration: 1.5 mg/day increments	0.93	0.50–1.88	0.930			

*corrected for age and gender; CI = Confidence Interval; MMSE = Mini Mental State Examination; MAD = Maximum Achieved Dose; OR = Odds Ratio.

($n = 11$). Of 154 started patients, 23 users were still continuing therapy by September 2004, ranging from less than 12 months to more than 42 months of treatment.

Risk factors for discontinuation within the first half year

As can be observed in Table 1, the 61 patients who discontinued therapy within the first 6 months had a lower MAD ($p < 0.001$), were less educated and were less frequently supported by a nurse ($p < 0.05$) in comparison to the patients who continued therapy.

Results of the logistic regression analysis are shown in Table 3. The multivariate analysis showed that a MAD of 1.5–4.5 mg daily (OR 11.6, 95% CI 3.65–37.00 $p < 0.001$) and no nurse support (OR 2.22, 95% CI 1.05–4.73, $p = 0.038$) appeared to be independent predictors of discontinuation within the first half year.

DISCUSSION

Rivastigmine was frequently discontinued, because of intolerable adverse events during the first 6 months of treatment and thereafter mainly for ongoing deterioration. Discontinuation within the first 6 months was significantly related with a MAD of 1.5–4.5 mg daily and absence of nurse support.

The comparison of our results to those described in the literature has limitations. It is difficult to compare cholinesterase studies, because designs are substantially different (Anand *et al.*, 2003). Rivastigmine was evaluated in two large randomised placebo-controlled trials during 26 weeks which were subdivided into low (<6 mg/day) and high (6–12 mg/day) dose groups (Corey-Bloom *et al.*, 1998; Rösler *et al.*, 1999). In the Newcastle (UK) study, four of 26 patients (15.4%) discontinued rivastigmine therapy because of side effects within the first 4 weeks of treatment (Pakrasi *et al.*, 2003). As we did not investigate discontinuations in this period direct comparisons fall short. An Austrian study, however, followed 529 patients in usual care over 24 weeks. This period is comparable to our cohort, which was followed for 26 weeks. In the Austrian study there were 67 drop-outs (12.7%) of whom 40.3% experienced side effects (Schmidt *et al.*, 2002). Thirty-nine patients were able to continue treatment although not achieving doses of 6 mg daily, which was not possible in our design and partly explains differences in number of discontinuations.

As earlier described, patients are urged not to continue therapy if titration to 6 mg daily failed and explains a daily MAD < 6 mg as an independent predictor of discontinuation in our clinical setting. Absence of nurse support, also an independent predictor, can be explained because adverse events and changes in titration-rate are discussed in regular telephone calls between the nurse and relatives or close friends of rivastigmine users. Strengths of our study are a relatively large population in a naturalistic setting, a total follow-up time of 42 months and accessibility to all relevant clinical data.

In conclusion, initially discontinuation for intolerable adverse events is of major concern. Support by a nurse is important in this first period. After the first period the major reason for discontinuation is an ongoing decline in cognition, performance or behaviour.

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