

SHORT REPORT

Prediction of treatment response to rivastigmine in Alzheimer's dementia

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Objectives: To predict the treatment response to rivastigmine in patients with Alzheimer's dementia using neuropsychological and EEG data.

Methods: A neuropsychological examination and a quantitative EEG study were done in 20 patients with Alzheimer's dementia before initiating treatment with rivastigmine. After one week of treatment a second EEG examination was done. Therapeutic efficacy was determined six months after treatment initiation. Treatment response was defined as improvement in short term memory after six months of rivastigmine treatment.

Results: For the group of patients as a whole, there was a significant improvement in short term memory and orientation during rivastigmine treatment. The mini-mental state score improved from 20.2 to 21.7 (NS). In the EEG, theta power decreased significantly after one week of treatment. Treatment responders had a greater decrease in theta power after one week of treatment and a better short term memory at baseline than non-responders. Decrease in theta power during rivastigmine treatment and baseline short term memory were good predictors of treatment response.

Conclusions: Generally available neuropsychological and EEG data may be useful for predicting response to rivastigmine in patients with Alzheimer's disease.

Treatment with cholinesterase inhibitors is beneficial for patients with Alzheimer's dementia, although the average benefit appears to be small.¹ The rationale for the efficacy of these agents is the cholinergic hypothesis of Alzheimer's disease, attributing the decline in learning and memory to a cholinergic deficit mediated by impairments of excitatory amino acid neurotransmission and attentional processing.²

Rivastigmine is a modern cholinesterase inhibitor with established therapeutic efficacy.³ Rivastigmine treatment has also been shown to affect glucose metabolism, as assessed by positron emission tomography,⁴ functional magnetic resonance imaging,⁵ magnetencephalography⁶ and quantitative spectral EEG analysis.⁷ In the EEG, rivastigmine produces a decrease in slow wave power in the theta and delta frequency bands, which may be directly related to the amelioration of the cholinergic deficit.⁸

In clinical practice it can be observed that about half the patients treated with cholinesterase inhibitors show a visible improvement in cognitive performance within weeks or months, whereas in the other half, no improvement (that is, no obvious benefit of treatment) can be ascertained. On the other hand, cholinesterase inhibitor treatment is associated with important side effects and costs.

Until now, no predictors of a therapeutic response to cholinesterase inhibitors in Alzheimer's disease have been

identified. Recent findings suggest that the therapeutic efficacy of rivastigmine is particularly good in patients fulfilling the criteria of dementia with Lewy bodies, in which cholinergic deficit, vigilance impairment, and EEG alterations are major features.⁹ Increased EEG slow wave activity in patients with Alzheimer's disease probably reflects a cholinergic deficit. Consequently, effective cholinesterase inhibitor treatment should lead to a decrease in EEG slow wave activity. We therefore examined whether the short term effect of rivastigmine on quantitative EEG indices in Alzheimer's disease could be useful in predicting the therapeutic efficacy of this drug. Twenty patients with Alzheimer's disease were considered sufficient for a first analysis.

METHODS

The study was conducted in patients who had probable Alzheimer's disease according to NINCDS-ADRDA criteria.¹⁰ It was a requirement that they had no evidence or history of neurological disease, no contraindication to treatment with cholinesterase inhibitors, and were on no other psychopharmacological treatment. Computed tomography or magnetic resonance imaging of the brain should be within normal limits or should reveal only atrophy or minor vascular lesions without clinical significance.

Before initiation of treatment with rivastigmine, cognitive performance was assessed by the mini-mental state examination (MMSE)¹¹ and the structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia, and dementias of other aetiology (SIDAM).¹² Functional level was assessed by the Barthel index¹³ and the instrumental activities of daily living scale (IADL).¹⁴ An EEG was recorded for quantitative spectral analysis according to a previously described method.⁷ One week after the initiation of treatment, a second EEG recording was done. Six months later cognitive performance and functional level were again assessed.

The study was approved by the ethics committee of the Mannheim Medical Faculty of Heidelberg University.

Statistics

The significance of differences in cognitive performance, functional level, and quantitative EEG indices was determined using paired Student *t* tests after having ascertained a normal distribution. As positive treatment effects on cognitive performance and functional level and a normalisation of EEG indices were expected, the levels of significance were calculated for one sided tests. Analyses were restricted to the

Abbreviations: GDS, global deterioration scale; IADL, instrumental activities of daily living scale; MMSE, mini-mental state examination; SIDAM, structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia, and dementias of other aetiology; SISCO, SIDAM score

fully evaluable population—that is, the patients in whom the entire initial and follow up assessments could be carried out and who had been continuously under rivastigmine treatment. Data acquisition was finished when we obtained a fully evaluable population of 20 patients. Values are given as mean (SD).

RESULTS

We initiated the study in 26 patients. After six months, five of these had discontinued treatment, mainly because of side effects, while one patient was lost to follow up because she had moved to another town. Thus the fully evaluable population was made up of 20 patients, 15 women and five men, aged between 67 and 85 years (mean (SD), 73.9 (4.8) years). Their MMSE scores ranged between 13 and 28 (mean, 20.2 (4.6)); global deterioration scale (GDS) scores¹⁵ were between 3 and 5 (mean, 4.1 (0.7)). The values for the SISCO (SIDAM score) and the SIDAM syndromes are given in table 1. Mean Barthel index and IADL score were 92 (15) and 5.5 (1.9), respectively.

Treatment was initiated with a daily dosage of 3 mg rivastigmine. This dose was maintained for two weeks and subsequently increased. One week after the initiation of treatment, we found a significant decrease in global theta power. In 15 patients theta power was reduced, while in five it was unchanged or increased. The mean values for the global spectral EEG powers are given in table 1. At the six month follow up, the patients were being treated with either 3 mg rivastigmine daily (n = 4), 6 mg daily (n = 9), or 9 mg daily (n = 7). We found a significant improvement in the SIDAM syndromes "short term memory" and "orientation"; the MMSE score only showed a trend to improvement (increasing from 20.2 to 21.7). The values are given in table 1. Functional level was not significantly improved.

When defining therapeutic response rather restrictively as an improvement in short term memory after six months of rivastigmine treatment, eight of the 20 patients (40%) were classified as responders and 12 as non-responders. In the responders, theta power had substantially decreased after one week of rivastigmine treatment, in contrast to the

non-responders, in whom there was no decrease: -27.3 (24.7) ν 0.8 (10.0) μV^2 ; $t = 3.566$, $p = 0.002$. With respect to baseline characteristics, the only significant difference between responders and non-responders was that the former had a higher score in the SIDAM syndrome "short term memory" (2.4 (1.8) ν 0.7 (1.0); $t = -2.702$, $p = 0.015$). Application of both indices as independent variables in a logistic regression analysis allowed a completely correct prediction of responders and non-responders. If theta power decrease and pretreatment short term memory were each applied as single predictors, logistic regression analysis revealed an explained variance of 50.0% and 37.5%, respectively.

DISCUSSION

For the entire patient group, performance in the SIDAM syndromes "short term memory" and "orientation" was significantly improved under rivastigmine treatment. There was only a trend to improvement in the MMSE score. The non-significance of the improvement of global indices of cognitive performance and functional level, in contrast to other studies (for example, Rösler *et al*¹⁶) may be attributed to the low sensitivity of the instruments applied and to the comparatively small number of subjects studied. However, the goal of this study was not to demonstrate the general effectiveness of rivastigmine treatment but to identify predictors of a therapeutic response. With respect to EEG spectral analysis, we found a significant decrease in global theta power during rivastigmine treatment, in line with previous findings on rivastigmine⁷ and other cholinesterase inhibitors.¹⁷⁻¹⁹

Applying improvement in short term memory after six months of rivastigmine treatment as the response criterion, eight of 20 patients (40%) were classified as responders. In the responders, the EEG theta power decrease after one week of rivastigmine treatment was significantly greater than in the non-responders. This is in good agreement with previous observations during tacrine treatment, where a decrease in EEG slow wave activity under a test dose of tacrine predicted a good therapeutic response.^{20,21} Furthermore, treatment

Table 1 Cognitive performance and EEG frequency spectrum before and under rivastigmine treatment

	Before treatment	Under treatment	t Value	p Value
<i>Cognitive performance</i>				
MMSE	20.2 (4.6)	21.7 (4.9)	-1.607	0.063
SISCO	34.0 (8.4)	35.4 (8.4)	-1.006	0.163
SIDAM				
Orientation	6.5 (2.5)	7.3 (2.2)	-1.824	0.042
Recall	4.2 (0.9)	4.4 (0.7)	-1.258	0.107
Short term memory	1.4 (1.6)	2.0 (2.5)	-2.221	0.020
Long term memory	4.4 (1.7)	4.1 (1.6)	1.165	0.129
Memory	10.0 (2.9)	10.5 (3.2)	-0.930	0.182
Intellectual capabilities	3.9 (1.3)	3.7 (1.4)	0.719	0.241
Verbal and calculation capabilities	4.1 (2.2)	4.3 (2.1)	-0.507	0.309
Visuospatial capabilities	1.2 (1.2)	1.3 (1.0)	-0.271	0.395
Aphasia and apraxia	8.3 (1.6)	8.3 (2.0)	0.000	0.500
Higher cortical functions	13.6 (3.8)	13.9 (3.5)	-0.216	0.415
<i>EEG frequency spectrum</i>				
Delta power (μV^2)	27.6 (26.4)	26.7 (29.7)	0.165	0.435
Theta power (μV^2)	54.9 (65.3)	44.4 (57.7)	2.138	0.023
Alpha power (μV^2)	50.6 (49.2)	40.6 (45.2)	1.489	0.076
Beta power (μV^2)	27.7 (27.4)	22.3 (22.0)	1.239	0.116

MMSE, SIDAM, and SISCO scores and EEG spectral frequency powers are given as means (SD). Values of *t* and *p* were calculated using paired one sided Student *t* tests. Significant values in bold.

Reassessment of MMSE, SIDAM, and SISCO was undertaken after six months of rivastigmine treatment. The second EEG recording was obtained after one week.

MMSE, mini-mental state examination; SIDAM, structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia, and dementias of other aetiology; SISCO, SIDAM score.

responders had a better pretreatment short term memory performance than non-responders. This may indicate that a certain minimum of short term memory performance or underlying cholinergic function is required for a measurable therapeutic effect of cholinesterase inhibitors. It also underlines the need for early recognition of Alzheimer's disease in order to allow timely initiation of cholinesterase inhibitor treatment. Thus both conditions—accessibility of the cholinergic system for cholinesterase inhibitor treatment (reflected by the EEG) and sufficient preservation of cholinergic function (indicated by the remaining short term memory)—may be required to allow a measurable improvement in short term memory during rivastigmine treatment.

Short term memory and EEG spectral power can both be assessed using non-invasive, generally available procedures, which thus may allow reliable prediction of the likely therapeutic efficacy of rivastigmine in the individual patient. This could be particularly relevant for the treatment of Alzheimer patients with relative contraindications to cholinesterase inhibitors—mainly cardiac arrhythmias—and may even provide an indication for cardiac pacemaker implantation. On the other hand, short term memory is not the only variable relevant to the therapeutic efficacy of cholinesterase inhibitors, and there may be important therapeutic effects of these agents that are only modestly or even not at all associated with measurable cognitive improvement.^{22, 23} Thus further studies on the individual benefit of cholinesterase inhibitor treatment in Alzheimer's disease and its prediction will be required.

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