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Switch from selegiline to rasagiline is beneficial in patients with Parkinson's disease

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Abstract The objective of this study is to demonstrate that application of rasagiline instead of selegiline with concomitant determination of L-amphetamine and L-methamphetamine in plasma is safe and well tolerated and influences sleep, mood, and motor behavior in patients with Parkinson's disease on a stable drug therapy. 30 patients, who took 7.5 mg selegiline daily for at least 3 months, were switched to 1 mg rasagiline. Then they were followed over an interval of 4 months. The remaining drug therapy remained stable. This changeover was safe and well tolerated. L-Amphetamine and L-methamphetamine only appeared during selegiline treatment. Motor behavior, motor complications, mood and sleep improved during rasagiline administration. Amphetamine-like derivatives of selegiline could contribute to sleep disturbances, which may be involved in worsening of mood. Motor behavior and motor complications probably became better due to the additional glutamate receptor antagonizing properties of rasagiline in this open label study.

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Introduction

Patients with Parkinson's disease (PD) frequently suffer from non-motor symptoms. Disturbed sleep quality may result from reduced turning behavior and early morning akinesia due to an insufficient dopamine substitution at night. Accordingly, transdermal or extended release administration of dopamine agonists improved sleep quality, as these application modes also provided a more continuous drug supply during the night (Trenkwalder et al. 2010; Dusek et al. 2010). Dopamine substituting drugs may also induce fatigue or even so-called sleep attacks during daytime. Thus these compounds may alter sleep wake regulation in PD patients in the long term (Garcia-Borreguero et al. 2003). Certain PD drugs or their derivatives increase wakefulness and thus worsen sleep quality. The MAO-B inhibitor selegiline (Se) may represent such a compound, as Se is metabolized to desmethylselegiline and L-methamphetamine. Both pathway products are further degraded to L-amphetamine. Moreover, chronic treatment with Se additionally reduces the metabolism of Se and its derivatives, since both Se and its metabolite desmethylselegiline may inhibit or downregulate its own metabolic enzymes within the CYP 450 system (Siu and Tyndale 2008). Se and to a lesser extent desmethylselegiline belong to an acetylene group of compounds that contain a carbon–carbon triple bond. These substances are known to be potent mechanism-based inhibitors (Laine et al. 2000; He and Grasing 2006; Siu and Tyndale 2008). As a result the daily intake of Se hypothetically contributes to an accumulation of amphetamine-like compounds. They increase synaptic catecholamine release and deplete catecholamine

stores (Laine et al. 2000). One may also assume that a putative enrichment of amphetamine-like substances may particularly take place in the brain during repeated Se intake. It is known that Se is a non polar, weak organic base. Therefore Se quickly and efficiently penetrates into the brain (Laine et al. 2000). These pharmacological characteristics of Se are independent of MAO-B inhibition. But these findings initiated trials which demonstrated the efficacy of Se against narcolepsy, depression and attention deficit disorders (Thorpy 2007). In contrast to Se, the MAO-B inhibitor rasagiline (Ra) is metabolized to aminoindan (AI) (Chen et al. 2007). AI has no amphetamine-like properties and may even contribute to the efficacy of Ra (Bar-Am et al. 2010). In animal models of PD, AI has been shown to enhance striatal dopamine transmission. AI improved motor function, independent of MAO inhibition, although AI is a weak inhibitor of MAO-B (Brotchie et al. 2011). Moreover, preclinical studies suggest that AI contributes to the neuroprotective effects of Ra administration (Bar-Am et al. 2010). Both Ra and AI, but not Se antagonized NMDA receptor, AMPA receptor and metabotropic glutamate receptor mediated increase of neuronal transmission in a dose-dependent fashion in an in vitro trial with rat hippocampus slices, which investigated the pyramidal cell response after electric stimulation of the Schaffer collaterals. In the same experimental approach, only Se attenuated kainate receptor mediated increases of excitability (Dimpfel and Hoffmann 2011). These key differences in the pharmacology of Ra and Se support the notion that there are differences in the efficacy of non-motor symptoms and tolerability of the two drugs in PD patients. The objectives were to investigate the safety and tolerability of a switch from Se to Ra, to measure L-amphetamine and L-methamphetamine in plasma and to evaluate sleep-, mood- and motor behavior in PD patients during chronic Se therapy and then after the changeover from Se to Ra in this report of this pilot study.

Methods

Subjects

30 idiopathic PD patients participated in this trial. The patients' characteristics are given in Table 1. The therapy of selegiline with budipine or amantadine was monitored by ECG on a regular basis regarding QTc-time prolongation in addition to existing literature that describes these combinations as efficacious, safe and well tolerated (Przuntek et al. 2002) The participants fulfilled the clinical diagnostic UK Brain bank criteria for PD and suffered from sleep disturbances to a certain extent at baseline (Table 1). Exclusion criteria were unpredictable fluctuations.

Design

This was a trial in one center only. Ratings were performed by one physician. The d_2 test and blood sampling were done by technicians. Participants were switched from a daily, in Germany mostly used dose of 7.5 mg Se (day A: last day of Se administration), taken for at least 3 months, to 1 mg Ra in an open label fashion. The remaining drug therapy was stable over the whole study interval. The PD patients were again investigated 2 months (day B) and 4 months (day C) after the change to Ra (Table 2).

Blood sampling and assessment

Blood samples were taken before and 2 h after intake of the MAO-B-inhibitor. Blood specimen were at once centrifuged, then decanted and stored at −80 °C. The period between freezing and work up of the plasma samples was no longer than 3 months. L-Methamphetamine and L-amphetamine were determined by high-performance liquid chromatography (Nishida et al. 2006).

Clinical evaluation

Ratings were executed two hours after drug intake on each investigation day and included the performance of the Parkinson's Disease Sleep Scale (PDSS), the Hamilton Depression Scale (HAMD), the Unified Parkinson's Disease Rating Scale (UPDRS) and the Parkinson's Disease Questionnaire (PDQ 39) and the d_2-Test, which evaluates attention load in an objective and standardized manner (Brickenkamp 2002), in a defined, consecutive order.

Table 1 Patient's characteristics and drugs for the treatment of PD

Age	66.6 ± 6.5 years
Sex	18 men, 12 women
Hoehn yahr stage	2.1 ± 0.07
Mini mental status examination	28.17 ± 0.75
Concomitant PD drug therapy	Number of patients
Levodopa	14
Lisuride	1
Pramipexole	11
Cabergoline	7
Pergolide	8
Entacapone	1
Budipine	12
Amantadine	22

Data are given as mean ± standard error of mean, if applicable

Table 2 Outcomes of rating scales before and after switch from selegiline to rasagiline

Line	Scale/test	A	B	C	F	*p*	A versus B	A versus C
1	UPDRS	22.63 ± 1.79	22.07 ± 1.79	21.40 ± 1.86	3.95	0.02	ns	0.0068
2	UPDRS III	14 ± 1.24	13.73 ± 1.22	12.97 ± 1.25	3.85	0.03	ns	0.0098
3	UPDRS IV	1.37 ± 0.12	0.93 ± 0.13	0.77 ± 0.11	14.42	<0.001	<0.001	<0.001
5	HAMD	8.07 ± 0.6	7.10 ± 0.62	6.87 ± 0.65	5.24	0.01	0.017	0.003
4	PDSS	111.33 ± 2.85	124.94 ± 2.22	126.01 ± 2.04	25.32	<0.001	<0.001	<0.001
6	d_2	6.54 ± 0.55	7.21 ± 0.56	7.16 ± 0.62	3.96	0.025	0.01	0.02
7	PDQ 39	24.61 ± 2.8	22.42 ± 2.14	22.60 ± 2.59	1.79	ns	ns	ns

Data are given as mean ± standard error of mean

ns not significant, *d_2* d_2-test outcomes, *DF F*-value of the ANOVA analysis, *p p*-value of the ANOVA, *A versus B p* value of the post hoc analysis between days A and B, *B versus C p*-value of the post hoc analysis between days B and C, *PDQ 39* Parkinson's Disease Questionaire, *PDSS* Parkinson's Disease Sleep Scale, *HAMD* Hamilton Depression scale, *UPDRS* total score of the Unified Parkinson's Disease Rating Scale, *UPDRS I* Unified Parkinson's Disease Rating Scale part mental behavior, *UPDRS II* Unified Parkinson's Disease Rating Scale part activities of daily living, *UPDRS III* Unified Parkinson's Disease Rating Scale part motor examination, *UPDRS IV* Unified Parkinson's Disease Rating Scale part motor complications

Statistics

ANOVA with a repeated measures design and the least significant difference test for the post hoc analysis were employed for the comparisons between outcomes of days A, B and C. The last observation carried forward method (LOCF) was used in case of missing data (PDQ 39: 1 time; d_2-test: 3 times). A *p* value below 0.05 was considered as significant in this exploratory statistical analysis of this observational pilot trial.

Ethics

All participants gave written informed consent. The study was approved by the local ethic committee (EudraCT-Nr.: 2008-002145-22).

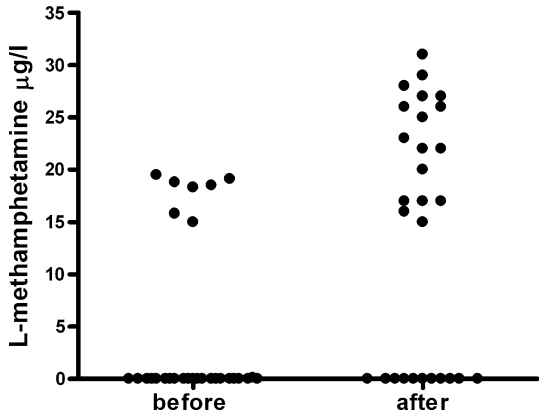

Fig. 1 Raw values of L-methamphetamine levels before selegiline application and 2 h after acute selegiline intake. µg/l (please note that only 29 values are reported, assessment was not performed in one patient due to technical reasons)

Results

L-amphetamine (day A: seven patients with a level of 0.1 (µg/l) before Se intake; 16 patients with a concentration of 0.1 2 h after oral Se intake) and L-methamphetamine (Fig. 1 b) were only found in plasma during Se treatment, but not under Ra therapy.

The switch to RA caused decay of the UPDRS total score and of the UPDRS III score. This effect was most pronounced on day C after 4 months of RA intake according to the post hoc analysis. The UPDRS IV score was better on days B and C in comparison to day A (see lines 1–3, Table 1). There were no further relevant changes for the better between month 2 and month 4 of Ra treatment, since no significant differences were found between days B and C in the post hoc analysis.

After the changeover to RA, there was an amelioration of depressive symptoms, as the HAMD scores went down (see line 4, Table 1). Sleep, reflected by the PDSS outcomes, and concentration, demonstrated by the d_2-test results, enhanced during Ra administration (see lines 5 and 6, Table 1). We observed no effect with the PDQ 39 scale (see line 7, Table 1).

The switch from Se to Ra was well tolerated, side effects did not occur.

Discussion

Generally, this open study validates the well-known safety and tolerability of MAO-B inhibitors in PD patients (Fernandez and Chen 2007). As expected, we confirm that amphetamine-like metabolites only occurred in plasma of PD patients during Se therapy, but not during chronic Ra intake (Kronstrand et al. 2003). We determined L-amphetamine and L-methamphetamine only in the

periphery. Therefore we cannot draw any conclusion on their putative brain accumulation. But it is known from experimental trials, that both irreversible MAO-B-inhibitors are pharmacological different as a result of their degradation modes (Laine et al. 2000; Lecht et al. 2007).

Our present clinical outcomes indicate that the occurrence of amphetamine-like substances during Se administration may exert a long-term effect on the onset and on the intensity of non-motor symptoms in PD patients. Accordingly, we observed moderately ameliorated rating scores directly and indirectly associated with better sleep quality after the replacement of Se by Ra. Particularly, the different metabolic turnover pathways of Ra and of Se hypothetically contributed to this finding. It is known that amphetamine and amphetamine-like compounds may reduce sleepiness (Antonini et al. 1997; Thorpy 2007). Therefore Se, administered in doses up to 20 mg daily, was effective in the treatment of narcolepsy (Roselaar et al. 1987; Mayer et al. 1995; Reinish et al. 1995). One may assume that amphetamine-like derivatives of Se worsen sleep quality by supporting onset of insomnia during chronic Se intake in PD patients. Sleep disturbances are related to a decrease of quality of life and of social and interpersonal functioning. All these factors could result in levels of distress or life events that may trigger, maintain, or worsen depressive symptoms. Insomnia also promotes a level of circadian misalignment that may also contribute to decrement in diurnal mood and performance (Taylor et al. 2003; Kahn-Greene et al. 2007; Buysse et al. 2008; Taylor 2008; Killgore 2010; Gregory et al. 2011; Roca et al. 2012). Accordingly we found higher HAMD scores during Se therapy and improved lower ones during treatment with RA. Generally sleep deprivation may influence different components of human attention not selectively, but particularly it decreases alertness. In this study PD patients showed better d_2-test outcomes during Ra administration. We assume that this results from better vigilance and concentration abilities as a consequence of improved sleep quality (Table 1) (Kahn-Greene et al. 2007; Killgore 2010; Roca et al. 2012).

There was also a better effect of Ra on the UPDRS total score compared with Se in our PD cohort. It is known that both Ra and Se moderately improve motor symptoms, reflected by the UPDRS III. Both compounds also ameliorate and delay the onset of motor fluctuations (Shoulson et al. 2002; Waters et al. 2004; Rascol et al. 2005). We found a beneficial effect on motor complications by Ra particularly observed 4 months after the switch. This finding may reflect experimental outcomes of an animal trial, which describes NMDA receptor antagonizing characteristics of Ra (Dimpfel and Hoffmann 2011). We admit that this improvement of UPDRS scores was found in an open label fashion. But this result may also indicate a certain long-term benefit of Ra therapy as a consequence of NMDA receptor modulation. It is known that NMDA receptor blockers enhance motor complications and have a moderate beneficial effect on motor symptoms in PD patients (Verhagen et al. 1998). We stress that performance of further clinical trials, for instance with the use of more specific rating scales for the evaluation of the degree of motor complications, is necessary to give further support for this hypothesis.

Generally we only found modest differences. We assume that this may be one reason for the not statistically significant, but mildly improved PDQ 39 scores in this trial. Therefore one may also hypothesize that the described ameliorations are not clinically relevant and may be of unclear clinical significance given the open label nature of the trial in particular (Hauser et al. 2011). Additionally we cannot exclude a certain impact of expectation and related reward in our study, since PD patients hoped to improve further by their participation due to the open switch to Ra. Similar findings were shown in experimental and clinical trials on the efficacy of placebo application in PD patients (Pollo and Benedetti 2009). Therefore we stress that further investigations with a placebo controlled, double dummy, crossover design should be performed to support our results. Moreover, more detailed pharmacokinetic trials are necessary to gain further information why both, L-amphetamine and L-methamphetamine, were not present in the plasma of all participating PD patients during Se application. One may also discuss that the detection limit of the determination procedure was too high to measure marginal concentrations of L-amphetamine and L-methamphetamine.

Conclusion

We show that a switch from Se to Ra is well tolerated and safe. This changeover may provide a certain benefit for PD patients in terms of occurrence of certain non-motor features and of motor behavior. This trial emphasizes that the choice of drugs for the treatment of motor behavior may also have implications on the appearance and the intensity of non-motor symptoms in PD.

Conflict of interest Thomas Müller, Walter Dimpfel and Christian Oehlwein received honoraria for the performance of this trial. Josef Hoffmann is an employee of TEVA pharmaceuticals.

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