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Lack of clinically significant interactions between concomitantly administered rasagiline and escitalopram

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ABSTRACT

Objectives: To evaluate the potential of pharmacodynamic and pharmacokinetic interactions of a concomitantly administered monoamine oxidase (MAO) type B inhibitor rasagiline and a selective serotonin reuptake inhibitor (SSRI) escitalopram.
Methods: Twelve healthy male volunteers received a 10-day regimen of rasagiline 1 mg daily, followed by concomitant rasagiline 1 mg and escitalopram 10 mg daily for 7 days.
Results: We found that the drug combination was generally well tolerated, and there were no signs of central nervous system hyperexcitation or changes in the subjects' vital signs. The reported adverse effects were mainly mild or moderate, and typical for SSRIs. The MAO-A-dependent catecholamine metabolite DHPG levels did not change significantly during the study suggesting that rasagiline's MAO-B selectivity was preserved. The plasma monoamine concentrations indicated no subclinical signs of interaction. As expected, the whole blood serotonin was significantly reduced by escitalopram but unaffected by rasagiline. Rasagiline AUC was increased by 42% ($p<0.0001$) and the weight-adjusted apparent oral clearance was reduced by 35% ($p=0.0009$) after 7 days' concomitant escitalopram treatment. Escitalopram reduced the ratio of the AUC values of the main metabolite 1-aminoindan and rasagiline by about 23% ($p=0.0079$). There were no significant changes in the elimination half-life, t_{max} and C_{max} of rasagiline.
Conclusions: These results suggest good tolerability of concomitant administration of rasagiline and escitalopram. However, other medications, diseases and aging may change the individual drug response and tolerability of concomitant rasagiline and escitalopram, e.g. in Parkinsonian patients, and thus careful monitoring is recommended when combining rasagiline and escitalopram.

1. Introduction

Rasagiline mesylate (N-propargyl-1(R)-aminoindan) is a second-generation, selective and irreversible inhibitor of monoamine oxidase (MAO) type B enzyme used in the treatment of Parkinson's disease (PD). The rationale of using MAO-B inhibitors in the treatment of PD is that they prolong the duration of action of both endogenous and exogenous dopamine. Rasagiline belongs to the family of propargylamines, the prototype of which is selegiline, the other MAO-B inhibitor in clinical use. Rasagiline has been found to be up to 10-fold more potent in inhibiting MAO-B than selegiline and, unlike selegiline, rasagiline is not metabolized into amphetamine derivatives (Chen et al., 2007; Youdim and Weinstock, 2002). Due to its non-amphetamine properties, rasagiline is suggested to have lesser psychiatric and cardiovascular side-effects and stronger neuroprotective effects than selegiline (Abassi et al., 2004; Am et al., 2004; Chen et al., 2007; Youdim and Weinstock, 2002). Rasagiline has been found efficacious in PD both as monotherapy in early disease and as adjunctive treatment in levodopa-treated patients with motor fluctuations (Chen et al., 2007).

Depression is common in patients with Parkinson's disease with prevalence rates up to 40% (Cummings and Masterman, 1999). Thereby, a definite need for safe and effective antidepressant treatment for this patient population exists. Selective serotonin reuptake inhibitors, SSRIs, have been considered as first-line therapy for PD patients with depression due to better tolerability and lesser anticholinergic side-effects in comparison to the traditional tricyclic antidepressants (Cummings and Masterman, 1999). SSRIs have generally been found efficacious in treating depressive symptoms in PD (Rampello et al., 2002; Zesiewicz and Hauser, 2002). Although case

Abbreviations: AE, adverse event; AUC, area under the concentration–time curve; CYP, cytochrome P450; DOPAC, dihydroxyphenylacetic acid; DHPG, 3,4-dihydroxyphenylglycol; HPLC, high-performance liquid chromatography; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; MS, mass spectrometer; MAO, monoamine oxidase; PD, Parkinson's disease; RP, reversed-phase; SSRI, selective serotonin reuptake inhibitor; 5-HT, serotonin.

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reports have described worsening of motor symptoms when SSRIs are introduced, it has not been confirmed in population studies (Zesiewicz and Hauser, 2002). However, the safety of the concomitant use of serotonin-enhancing agents and MAO-inhibitors has been questioned due to serious adverse drug interactions leading to serotonin toxicity (Chen et al., 2007; Dams et al., 2001; Keltner and Harris, 1994; Neuvonen et al., 1993; Taylor and Duncan, 1994). Most of the cases of serious interactions have occurred with inhibitors of the type A MAO enzyme, which is responsible for deactivating circulating catecholamines and dietary vasopressors (*i.e.* tyramine) in the gastrointestinal tract (Boyer and Shannon, 2005). The type B MAO enzyme, instead, mediates the breakdown of dopamine into dihydroxyphenylacetic acid (DOPAC) and further into homovanillic acid (HVA) in the brain (Chen et al., 2007). However, caution is recommended also when using MAO-B inhibitors since they can lose their selectivity if their blood concentration rises in consequence of, for example, a pharmacokinetic drug interaction. Based on the pharmacokinetic properties of rasagiline and escitalopram, a significant pharmacokinetic interaction is unlikely.

No cases of serotonin syndrome have been reported in rasagiline clinical trials to date (Teva Pharmaceutical Industries Ltd; data on file; Oldfield et al., 2007; Panisset et al., 2007). In a subgroup analysis of a randomized placebo-controlled trial of rasagiline in levodopa-treated patients with PD, *i.e.* the PRESTO study, there were no significant differences in the prevalences of adverse events (AEs) between rasagiline-treated patients with ($n=77$) or without ($n=395$) concomitant SSRI medication. In addition, among patients receiving SSRIs, there were no differences in the prevalences of AEs between those who received rasagiline and those who received placebo (Schwid and the Parkinson Study Group, 2005). In an analysis of data from all rasagiline-treated patients in controlled clinical trials ($n=1361$) who received any type of antidepressant ($n=323$) no apparent cases of serotonin syndrome were found (Panisset et al., 2007).

We set out to investigate the potential of pharmacodynamic and pharmacokinetic interactions between rasagiline and escitalopram in a clinical sequential setting with healthy volunteers.

2. Methods

2.1. Subjects

Twelve healthy Caucasian male volunteers aged 20–36 years and with body mass indexes 19–26 participated in this study. The subjects were ascertained to be healthy by medical history, physical examination and routine laboratory tests. Their urine was screened for illicit drugs. All the subjects were non-smokers and non-users of any nicotine-containing products. Besides an occasional paracetamol up to 1500 mg per day when needed, the subjects were not allowed to have any medications or herbal products for two weeks prior and during the study period. Alcohol, caffeine and grapefruit products were forbidden during and for two days before and after the study period. Tyramine-rich food, such as yogurt, aged cheese and processed meats, was advised to be avoided during the study period. The subjects were informed on the study both verbally and in writing, and a written informed consent was obtained. The study protocol was approved by the Ethics Committee of the Hospital District of Varsinais-Suomi, Finland, and the National Agency of Medicines, Finland.

2.2. Protocol

This study was conducted in an open, sequential setting, where the subjects received rasagiline 1 mg per day for ten days followed by concomitant escitalopram 10 mg per day for another 7 days to attain steady-state for both drugs (Fig. 1). In general, the subjects were treated as outpatients, however, on study days −1, 10, 11 and 17 they were admitted in the study ward. In addition, in the morning of day 4, the subjects visited the study site for safety measurements. On these above mentioned days (4, 10, 11, 17) the study medications were administered by the investigator at 9 am. On other days, the medication was self-administered in the morning between 8 am and 9 am, and to control adherence to the dosing schedule the subjects reported to the investigator of having taken the drugs every day by a text message. At the times subjects were not admitted to the study ward, there was a physician on call for 24 h per day.

Fasting for at least 10 h and refraining from physical exercise were required before study days −1, 10 and 17. On these days, a standard lunch was served 4 h after drug intake. A forearm vein was cannulated for blood sampling on days −1, 10 and 17. Timed venous blood samples for assessment of plasma concentrations of rasagiline and its main metabolite 1-aminoindan were drawn before and 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h after drug intake on days 10 and 17. In addition, repeated blood samples were collected for plasma concentrations of adrenaline, noradrenaline, the MAO-A-dependent catecholamine metabolite 3,4-dihydroxyphenylglycol (DHPG), a dopamine metabolite dihydroxyphenylacetic acid (DOPAC) and the anterior pituitary hormone prolactin. Concentrations of serotonin (5-HT) and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) were assessed from whole blood samples. The monoamine and prolactin concentrations were measured on days −1, 10 and 17. Blood samples for adrenaline, noradrenaline, DHPG and DOPAC were drawn at 0 (*i.e.* before drug administration) and 1, 2, 3, 4 and 6 h, for prolactin at 0, 0.5, 1, 2, 3 and 6 h and for 5-HT and 5-HIAA at 0 and 4 h. The samples were collected into chilled lithium-heparin (rasagiline and 1-aminoindan) or EDTA tubes (monoamines and prolactin) and handled at +4 °C. Plasma was separated within 30 min and stored at −20 °C (rasagiline and 1-aminoindan) or at −70 °C (monoamines and prolactin) until

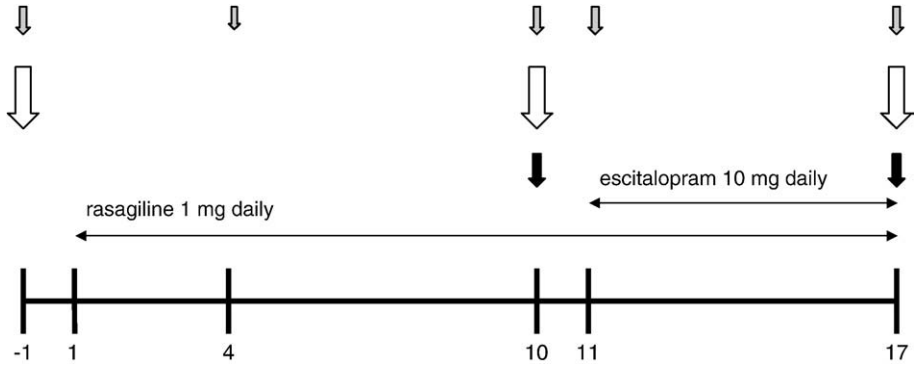

Fig. 1. The flow chart of the study. Black arrows indicate the measurement of rasagiline and 1-aminoindan concentrations, white arrows the measurement of monoamine (adrenaline, noradrenaline, DHPG, DOPAC, 5-HT, 5-HIAA) and prolactin concentrations, and grey arrows the questioning of adverse effects and measurement of blood pressure, heart rate and body temperature.

analyzed. The whole blood samples for 5-HT and 5-HIAA were stored at −70 °C immediately after sampling.

The subjects were questioned about adverse events by the same investigator in a standardized manner on days −1, 10, 11 and 17 at 0, 3 and 6 h and, additionally, once in the morning of day 4 as a safety measure. A two-part questionnaire was used. In the first part the subject was asked a passive question of how he feels, whereas in the second part he was actively inquired for specific symptoms of dizziness, dryness of mouth, weakness, fever, headache, incoordination, increased sweating, nausea, restlessness, tremor, muscle stiffness, tiredness and sleeping disturbances. All reported or otherwise noted adverse events were classified (score) as mild (1), moderate (3) or severe (5). If the severity of an ongoing symptom varied within the study, the highest ranking was used in the analysis. Blood pressure, heart rate and body temperature were measured at the same time points as the subjects were questioned about the AEs. Blood pressure and heart rate were measured after 5 min of sitting and always prior to possible blood sampling.

2.3. Analytical methods

The plasma concentrations of rasagiline and 1-aminoindan were measured at the bioanalytical laboratory of Teva Pharmaceutical Works Private Ltd. Co. in Debrecen, Hungary, using a validated reversed-phase(RP)-high-performance liquid chromatography (HPLC)/mass spectrometer(MS)-MS method in a calibration range of 75–15,000 pg/mL for rasagiline and 125–15,000 pg/mL for 1-aminoindan. The interassay coefficient of variation measured from quality control samples was less than 6% at relevant concentrations for rasagiline and 1-aminoindan. The lower limit of quantification was 75 pg/mL for rasagiline and 125 pg/mL for 1-aminoindan (Teva Pharmaceutical Industries Ltd, data on file).

The plasma concentrations of adrenaline, noradrenaline, DHPG and DOPAC as well as the whole blood concentrations of 5-HT and 5-HIAA were measured via HPLC using coulometric electrochemical detection (Scheinin et al., 1991). The interassay coefficients of variation were less than 10% at relevant concentrations for all monoamine analyses. The quantification limits were 0.10 nmol/L for adrenaline and noradrenaline, 0.50 nmol/L for DHPG, 2 nmol/L for DOPAC, 20 nmol/L for 5-HT and 2 nmol/L for 5-HIAA. Except for adrenaline, all the concentrations were clearly above the quantification limits. The analysis of one subject's 5-HIAA concentration from day −1 (4 h) and one subject's DHPG concentrations from day 17 (3, 4 and 6 h) were unsuccessful and the sample volume was insufficient for reanalysis. Therefore, only 11 subjects were available for assessments of the areas under the concentration–time curves (AUCs) of 5-HIAA on day −1 and DHPG on day 17.

The prolactin concentrations were analyzed with a commercially available radioimmunoassay kit (Prolactin IRMA, Orion Diagnostica, Espoo, Finland) with a quantification limit of 50 mIU/L. The interassay coefficients of variation did not exceed 12%. The measurements of the monoamine and prolactin concentrations were performed at the Clinical Research Services Turku (CRST) in subordination of the University of Turku in Turku, Finland.

2.4. Pharmacokinetic calculations

The pharmacokinetics of rasagiline and 1-aminoindan were characterized by determining the areas under the concentration–time curves ($AUC_{0-\infty}$ for rasagiline, AUC_{0-8h} for 1-aminoindan) calculated using the trapezoidal method, peak plasma concentrations (C_{max}) and the time from drug intake to peak concentration (t_{max}). The AUC values of 1-aminoindan could not be extrapolated to infinity for all subjects and thus, AUC_{0-8h} was calculated for rasagiline for determination of the ratio of the 1-aminoindan and rasagiline AUCs (*i.e.* AUC ratio). The weight-adjusted apparent oral clearance (clearance/weight) was determined for rasagiline. The pharmacokinetics of adrenaline, noradrenaline, DHPG, DOPAC and prolactin were described by determining the AUCs from 0 to 6 h. The mean concentrations of the two measurements were determined for 5-HT and 5-HIAA on study days −1, 10 and 17. The pharmacokinetic analyses were performed using the WinNonlin Professional program, version 4.1 (Pharsight Corporation, Mountain View, California, USA).

2.5. Statistical analysis

The analysis of variance for repeated measures was used if there were three or more evaluations and the paired *T*-test was used if there were two evaluations. *p* values of 5% or less were regarded as significant. The data which failed to fit the normal distribution was log-transformed prior to analysis. The data was analyzed using the SAS Enterprise Guide for Windows, version 3.0 (SAS Institute Inc., Cary, NC, USA).

3. Results

All subjects completed the study. One subject had one cup of coffee on day 9, and one subject took ibuprofen 600 mg on days 10 and 14 for wrist ache. One subject took the study medications at 7:30 am and 6:30 am on days 14 and 15. Otherwise, no protocol violations were observed. Plasma concentrations of rasagiline and the text messages received by the investigator suggested no lack of compliance in study drug intake.

3.1. Vital signs and adverse events

The concomitant administration of rasagiline and escitalopram was generally well tolerated. The most frequent adverse events during the whole study period were tiredness (in ten subjects), sleeping disturbances (in eight subjects) and headache (in six subjects) (Table 1). Other reported symptoms not listed in Table 1 were chesty/sore throat ($n=2$), mild allergic rhinitis plus cough ($n=1$) and ear ache ($n=1$) during rasagiline treatment. The scores reflecting the severity of a symptom were three-fold higher during the concomitant rasagiline–escitalopram treatment when compared to baseline or the rasagiline treatment alone (Table 1). All the symptoms reported at baseline or during the rasagiline treatment were rated as mild (61%) or moderate (39%). During the concomitant rasagiline and escitalopram treatment, one subject had severe headache and one

Table 1
Number of subjects with subjective adverse events at baseline (day −1), during rasagiline 1 mg daily (days 1–10) and during concomitant rasagiline 1 mg and escitalopram 10 mg daily (days 11–17).

Adverse event	Baseline	Rasagiline alone	Rasagiline + escitalopram
Dizziness		2 (1,1)	1 (1)
Dryness of mouth	1 (1)		
Headache	1 (3)	2 (3,3)	3 (1,3,5)
Nausea		1 (1)	3 (1,1,3)
Restlessness			1 (3)
Tremor			1 (1)
Muscle stiffness	1 (3)		
Tiredness	3 (1,1,3)	2 (1,1)	5 (1,1,1,3,5)
Sleeping disturbances	1 (3)	2 (1,3)	5 (1,1,3,3,3)
Loss of appetite			1 (3)
Stomach discomfort		2 (1,1)	2 (1,3)
Total number of events	7	11	22
Sum of ratings	15	17	48
Rating/event	2.14	1.55	2.18

Inquiries for adverse events were made at three time points at baseline, at four time points during rasagiline treatment, and at six time points during concomitant rasagiline and escitalopram treatment. Loss of appetite and stomach discomfort were spontaneously reported by the subjects, all other AEs were specifically inquired after. AEs subjectively rated as mild, moderate or severe were given a value of 1, 3 or 5, respectively. These ratings are shown in parenthesis.

subject had severe tiredness. The subject with severe headache had recurrent headache from day 4 forwards, usually a few hours after drug intake. All other symptoms during concomitant rasagiline and escitalopram were classified as mild (50%) or moderate (41%).

The systolic ($p<0.001$) and diastolic ($p<0.001$) blood pressures were moderately, but significantly lower during rasagiline treatment (mean 125/69 mm Hg) than at baseline (mean 130/73 mm Hg). During the concomitant escitalopram treatment the blood pressure values were returned near to the baseline values so that after a seven-day treatment with both escitalopram and rasagiline the systolic ($p=1.0$) and diastolic ($p=0.089$) blood pressures did not differ significantly from the baseline values (mean 129/71 mm Hg). The heart rate was slightly, but significantly lower during rasagiline–escitalopram treatment (mean 56 beats/min) than during rasagiline treatment (mean 58 beats/min, $p=0.0047$) or at baseline (mean 60 beats/min, $p=0.0097$). The body temperature did not change significantly during the treatments ($p=0.19$).

3.2. Plasma adrenaline, noradrenaline, DHPG and DOPAC

There were no significant differences in the AUCs of plasma adrenaline ($p=0.18$) and DHPG ($p=0.10$, Fig. 2) measured at baseline, after 10 days' treatment with rasagiline and after 7 days' treatment with both rasagiline and escitalopram. Instead, the AUC of plasma noradrenaline was significantly reduced from the baseline level after starting the study treatments ($p=0.0004$, Fig. 2). This reduction from the mean baseline AUC level of 6.9 nmol h/L to 5.8 nmol h/L after 10 days' rasagiline treatment was statistically not significant ($p=0.062$), but the further reduction to 4.4 nmol h/L after 7 days' rasagiline–escitalopram treatment differed significantly from the baseline values ($p<0.001$) and from the values measured after 10 days' rasagiline treatment ($p=0.0019$). The AUC of DOPAC was somewhat increased from baseline after 10 days rasagiline treatment and the increase was potentiated after the addition of escitalopram ($p=0.047$). In pairwise comparisons between the study days −1, 10 and 17 the differences were not, however, significant ($p=0.095$ between days −1 and 17; $p=0.23$ between days −1 and 10; and $p=1.00$ between days 10 and 17).

3.3. Whole blood 5-HT and 5-HIAA

The mean whole blood concentration of 5-HT was unaffected by the 10-day rasagiline treatment ($p=0.088$ vs. baseline), but dropped significantly after addition of escitalopram to the regimen for 7 days (Fig. 3). The 5-HT concentrations measured before study drug administration were similar to concentrations measured 4 h after

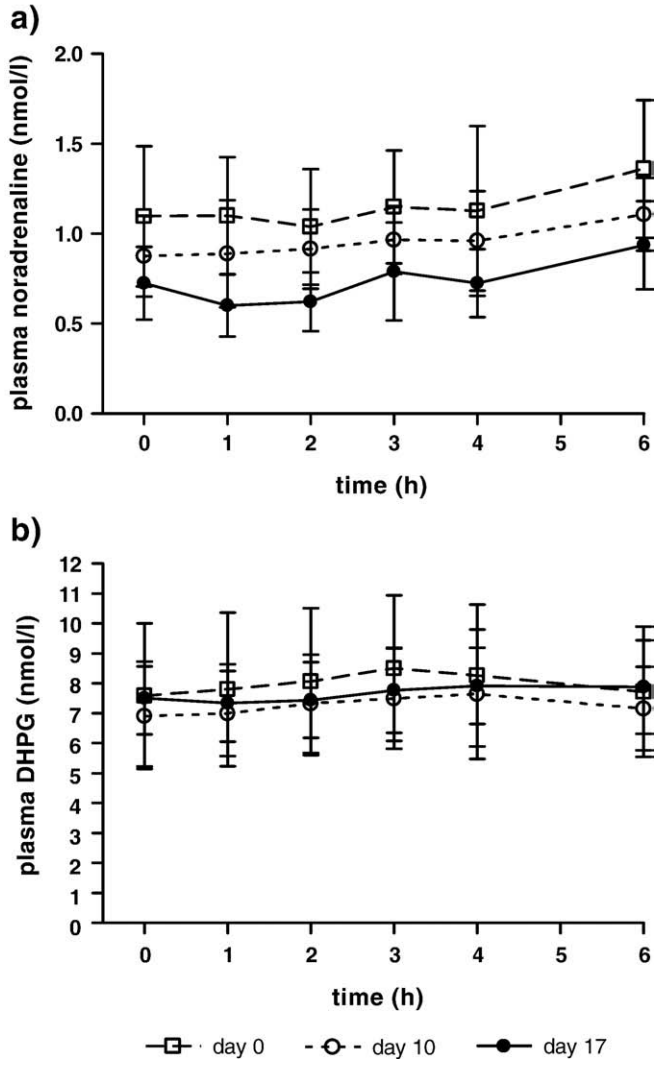

Fig. 2. Plasma concentrations (means ± SD) of noradrenaline (a) and 3,4-dihydroxyphenylglycol (b) at baseline (day −1), after rasagiline 1 mg once daily for 10 days (day 10) or after concomitant rasagiline 1 mg and escitalopram 10 mg once daily for 7 days (day 17).

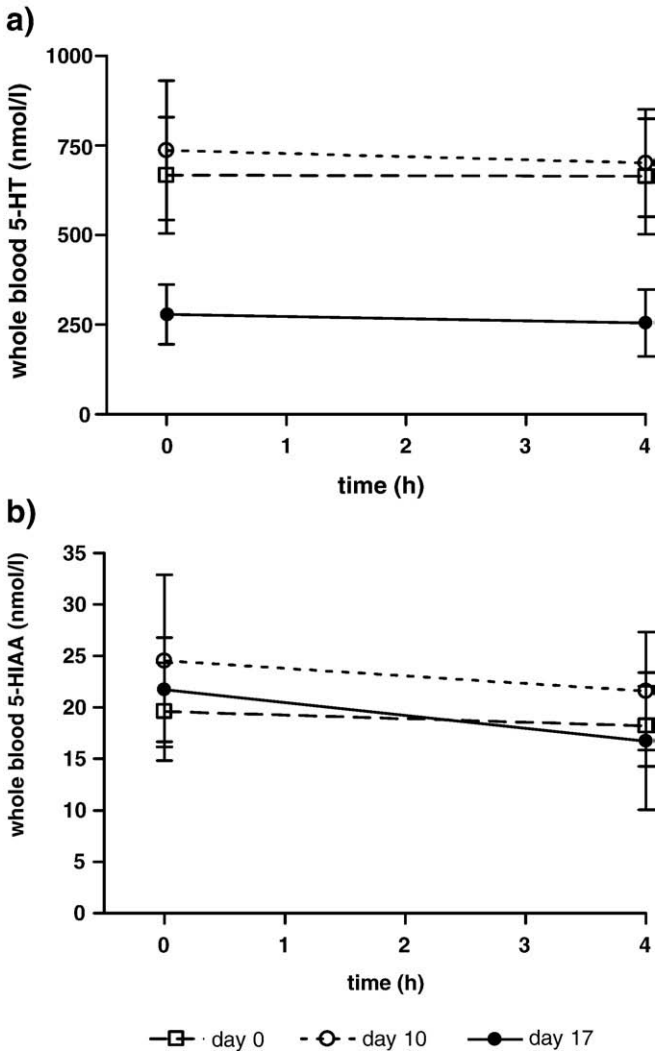

Fig. 3. Whole blood serotonin (5-HT) (a) and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) (b) concentrations (means ± SD) at baseline (day −1), after rasagiline 1 mg once daily for 10 days (day 10) or after concomitant rasagiline 1 mg and escitalopram 10 mg once daily for 7 days (day 17).

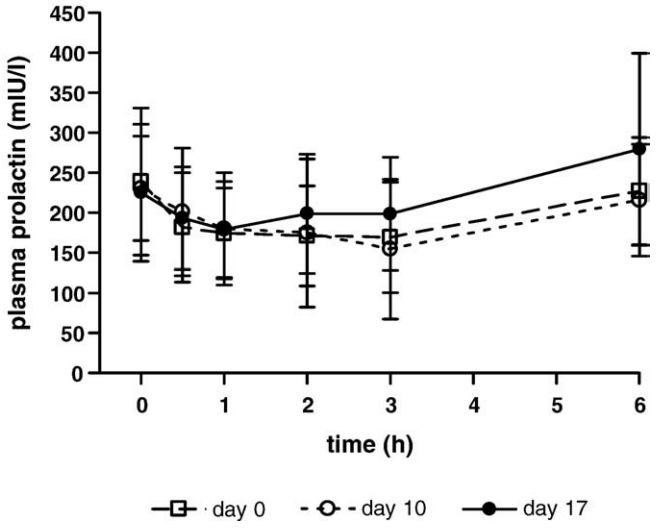

Fig. 4. Plasma prolactin concentrations (means ± SD) at baseline (day −1), after rasagiline 1 mg once daily for 10 days (day 10) or after concomitant rasagiline 1 mg and escitalopram 10 mg once daily for 7 days (day 17).

drug administration (p values from 0.15 to 0.89), but the mean 5-HT concentration was about 60% lower on day 17 vs. day −1 ($p<0.0001$) or day 10 ($p<0.0001$). The mean whole blood 5-HIAA concentration was slightly increased after the 10-day rasagiline treatment ($p=0.17$ vs. baseline), but returned to baseline levels after the 7-day rasagiline–escitalopram treatment ($p=1.00$ vs. baseline).

3.4. Plasma prolactin

The AUC of plasma prolactin was about 18% higher after 7 days' treatment with both rasagiline and escitalopram than after treatment with rasagiline alone ($p=0.031$, Fig. 4). This increase was not, however, significant when compared with the baseline prolactin AUC ($p=0.24$). Rasagiline treatment alone did not change the prolactin AUC significantly from the baseline ($p=0.84$).

3.5. Pharmacokinetics of rasagiline and its main metabolite 1-aminoindan

The mean rasagiline AUC was about 42% (range 2%–106%) higher after 7 days' treatment with both rasagiline and escitalopram than after 10 days' treatment with rasagiline alone ($p<0.0001$, Table 2, Fig. 5). The weight-adjusted apparent oral clearance of rasagiline was accordingly decreased by 35% after addition of escitalopram (day 17) when compared to rasagiline treatment alone (day 10) ($p<0.001$). The elimination half-life of rasagiline was not significantly affected by escitalopram ($p=0.088$). Also, the C_{max} ($p=0.21$) and t_{max} ($p=0.81$) of rasagiline were unaffected by escitalopram. After the addition of

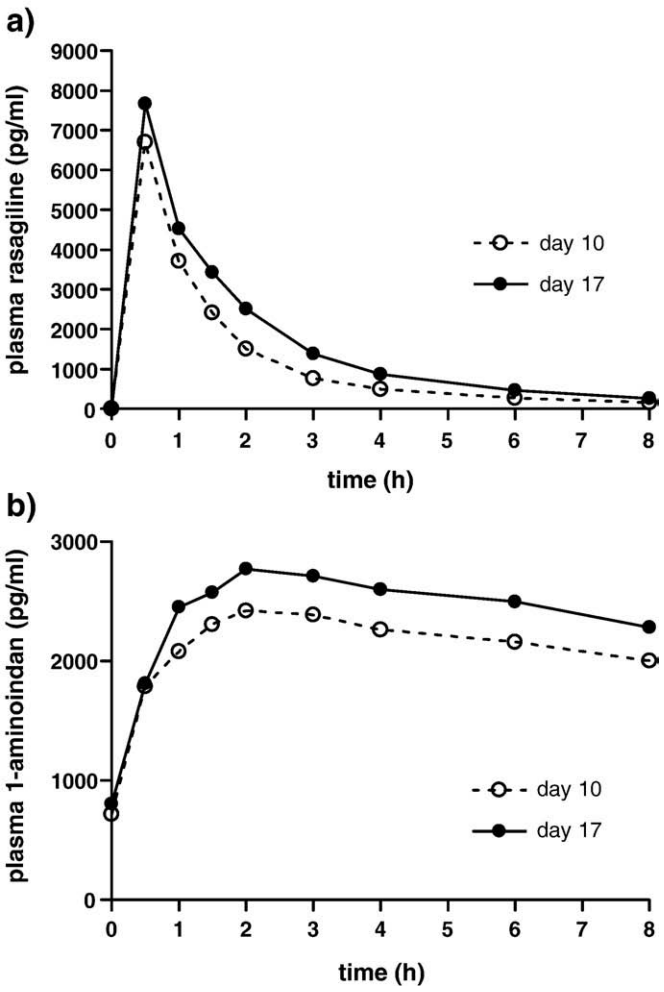

Fig. 5. Plasma concentrations (means) of rasagiline (a) and its main metabolite 1-aminoindan (b) after rasagiline 1 mg once daily for 10 days (day 10) or after concomitant rasagiline 1 mg and escitalopram 10 mg once daily for 7 days (day 17). Error bars have been omitted for clarity.

Table 2
Pharmacokinetics of rasagiline and its main metabolite 1-aminoindan after administration of 1 mg of rasagiline once daily for 10 days alone or with 10 mg of escitalopram once daily for additional 7 days.

Variable	Treatments		% difference between the treatments' mean values[a] (range)	Difference between the treatments
	Rasagiline alone	Rasagiline with escitalopram		
Rasagiline				
AUC (0–∞) (ng*h/mL)	9.9 ± 5.0	14.0 ± 6.2	+42% (2%–106%)	$p<0.0001$
C_{max} (ng/mL)	7.2 ± 2.9	8.3 ± 3.0	+14% (−58% to 94%)	$p=0.21$
t_{max} (h)	0.5 (0.5–1.5)	0.5 (0.5–1.5)	0 (−67% to 50%)	$p=0.81$
$t_{1/2}$ (h)	1.8 ± 0.32	2.0 ± 0.24	+9% (−18% to 50%)	$p=0.088$
Cl/F (L/h/kg)	1.6 ± 0.69	1.1 ± 0.31	−35% (−2% to −51%)	$p=0.0009$
1-Aminoindan				
AUC (0–8 h) (ng*h/mL)	17.2 ± 4.7	19.6 ± 5.1	+14% (−6% to 52%)	$p=0.017$
C_{max} (ng/mL)	2.7 ± 0.85	3.0 ± 0.78	+12% (−22% to 64%)	$p=0.11$
t_{max} (h)	2.0 (0.5–4.0)	2.0 (0.5–6.0)	0 (−75% to 1100%)	$p=0.61$
$t_{1/2}$ (h)	24 ± 17	16 ± 3.9	−35% (−72% to 99%)	$p=0.13$
AUC ratio (1-aminoindan/rasagiline)	2.1 ± 0.96	1.5 ± 0.56	−25% (−44% to 7%)	$p=0.0076$

Data is given as arithmetic mean ± arithmetic SD except for t_{max} data, which is given as median and range.
[a] Difference between the median values for t_{max}.

escitalopram into the treatment the mean 1-aminoindan AUC was about 14% higher than during rasagiline treatment (mean 19.6 ng h/mL vs. 17.2 ng h/mL, $p=0.017$). There were no significant differences in the C_{max} ($p=0.11$), t_{max} ($p=0.61$) and $t_{1/2}$ ($p=0.13$) values of 1-aminoindan before and after the addition of escitalopram. The ratio of the AUC values of 1-aminoindan and rasagiline (AUC ratio) was reduced by about 23% after starting the escitalopram treatment (mean 1.6 vs. 2.1; $p=0.0079$).

4. Discussion

Although no cases of serotonin syndrome have been reported in rasagiline clinical trials so far (Teva Pharmaceutical Industries Ltd; data on file; Panisset et al., 2007) and though results from tyramine challenge studies have indicated a wide tolerability margin for rasagiline and dietary tyramine (deMarcaida et al., 2006; White et al., 2008), the safety of the concomitant use of rasagiline and SSRIs has been questioned. In this study on healthy volunteers, but with a dosing regimen resembling the clinical use of rasagiline and escitalopram, we found no evidence of a clinically obvious interaction between the two drugs, as observed by unchanged or, at most, mildly changed vital signs. Also, the lack of any subjective signs referring to hyperexcitation of the central nervous system supports the assumption of safe co-administration of rasagiline and escitalopram. The adverse effects reported during co-administration of rasagiline and escitalopram, namely headache, nausea, sleeping disturbances, tiredness, loss of appetite, restlessness and tremor, are all typical for SSRIs and usually subside in a few weeks after starting the SSRI medication (Westenberg and Sandner, 2006). The 10-day rasagiline treatment alone was well tolerated.

A statistically significant reduction was seen in the plasma noradrenaline, but not in adrenaline, concentrations after 7 days co-administration of rasagiline and escitalopram (day 17). The change was however quite small in comparison to the interday and intraday variations in noradrenaline concentrations and was not reflected by any increase (rather decrease) in blood pressure and heart rate of the subjects. Rasagiline alone caused a small and non-significant effect on noradrenaline concentrations. No change was observed in the plasma DHPG concentrations, an indicator of MAO-A activity, suggesting lack of MAO-A inhibition by rasagiline alone or by the combination of rasagiline and escitalopram.

Despite the 10-day MAO-B inhibition by rasagiline the concentrations of DOPAC, a MAO-B-dependent metabolite of dopamine, were paradoxically slightly increased and this increase was somewhat potentiated by addition of escitalopram into the regimen. Based on theoretical assumptions, a decreasing effect on DOPAC was rather expected. However, the raised rasagiline AUC may have counterbalanced the changes, which were in actual fact minor as shown by no significant differences in DOPAC concentrations in pairwise comparisons between the study days. The 10-day rasagiline treatment did not affect the whole blood 5-HT concentration, which may provide further evidence for the lack of significant MAO-A inhibition by rasagiline. However, as expected on the basis of earlier studies with SSRIs (Epperson et al., 2001; Hughes et al., 1996), the inhibition of serotonin reuptake by escitalopram caused a significant (60%) decrease in the mean whole blood 5-HT concentration, without any notable change in the mean concentration of 5-HIAA.

A higher than 90% irreversible MAO-B inhibition is reached already after the third daily dose of rasagiline 1 mg (Chen and Swope, 2005) so that monoamine profiles from day 10 are expected to represent the full effect of rasagiline 1 mg daily. Monoamine profiles from day 17 are expected to represent a long-term situation after continuous use of the drug combination. Taken together, both the clinical and monoamine effects after co-administration of rasagiline and escitalopram resembled those found in an earlier interaction study between another MAO-B inhibitor, selegiline, and racemic citalopram, also suggesting a lack of clinically meaningful interaction (Laine et al., 1997).

Prolactin was additionally studied because SSRIs have been reported to sometimes cause hyperprolactinemia and, based on its dopaminergic properties, rasagiline might have some influence on prolactin as well. In this study plasma prolactin concentrations were mildly raised after co-administration of rasagiline and escitalopram (day 17) when compared with rasagiline alone (day 10) but the change was not significant when compared with the baseline values (day −1). Rasagiline alone did not cause a significant change in plasma prolactin concentration compared with baseline. The mildly increased prolactin levels after 7 days rasagiline–escitalopram treatment are in line with the previous finding with paroxetine, according to which increases in the plasma prolactin are only seen after prolonged SSRI administration (Cowen and Sargent, 1997).

We found that the addition of escitalopram increased the AUC of rasagiline by about 42%, the maximum individual increase in the exposure being 106%. However, no significant change could be seen in the C_{max} or half-life of rasagiline. This increase in rasagiline AUC is in line with the variability (up to 40%) that has been seen in clinical trials with rasagiline 1 mg, and is not expected to have any clinical impact (Teva Pharmaceutical Industries Ltd, data on file). Rasagiline is almost completely metabolized by the cytochrome P450 (CYP) system, mainly by the CYP1A2, the main metabolite 1-aminoindan being devoid of MAO-B inhibitory property (Chen and Swope, 2005). In this study, however, the AUC of 1-aminoindan was also increased, suggesting lack of significant CYP1A2 inhibition by escitalopram. However, the fact that the AUC ratio of 1-aminoindan and rasagiline was reduced by 25% during concomitant escitalopram treatment suggests that escitalopram may have inhibited the rasagiline metabolism at some, but clinically insignificant extent. Escitalopram has been found to have low potential for pharmacokinetic drug interactions. In *in vitro* test models, escitalopram and its metabolite have been shown to be negligible inhibitors of CYP1A2 (IC_{50} values >250 μM) (von Moltke et al., 2001). In one case report, however, co-administration of citalopram 40 mg/day with clozapine 400 mg/day led to clinical symptoms typical for clozapine toxicity. The symptoms disappeared and the clozapine plasma levels decreased when the citalopram dose was reduced to 20 mg/day suggesting a possible CYP1A2 or 3A4 inhibition by citalopram (Borba and Herderson, 2000). This was in contrast to the results from an open clinical study with 15 schizophrenic patients where no changes in clozapine concentrations were observed during concomitant administration of citalopram 40 mg per day (Avenoso et al., 1998).

An alternative explanation to the moderately increased exposure to rasagiline during escitalopram co-administration is that rasagiline had not reached the steady-state on the tenth day of administration. The short elimination half-life of rasagiline of about 2 h does not suggest problems in reaching steady-state in 10 days. Moreover, rasagiline half-life was unchanged by escitalopram co-administration. However, day 10 was chosen for assessment of rasagiline and 1-aminoindan concentrations based on the manufacturer's unpublished data according to which the pharmacokinetic steady-state of rasagiline is reached after nine or ten days of rasagiline administration (Teva Pharmaceutical Industries Ltd, data on file). In clinical trials, chronic administration of rasagiline 1 mg daily usually gives AUC values of the same magnitude (or slightly greater) than those seen in this 10-day study (Teva Pharmaceutical Industries Ltd). This discrepancy between the short half-life of rasagiline and long time to reach pharmacokinetic steady-state may be explained by gradually saturable tissue binding of rasagiline, as has been described for another irreversible MAO-B inhibitor, selegiline (Laine et al., 2000). Variations in the compliance of drug intake is also possible, but considered unlikely. Nevertheless, the lack of significant changes in the concentrations of the MAO-A-dependent catecholamine metabolite DHPG indicate that the modest changes in rasagiline pharmacokinetics did not affect its selectivity to MAO-B. Despite the change in pharmacokinetics, no corresponding changes in pharmacodynamics were seen. Taken

together, the increase seen in rasagiline AUC was relatively small, with unlikely impact on clinical safety.

This study was carried out on healthy young men with no concomitant medications. In the elderly, the situation is complicated by a slower metabolic capacity overall, other diseases and often multiple other drugs. As a consequence, the elderly are more susceptible to adverse events. Also, female patients may have slightly different drug responses, although hormonal and other differences between men and women diminish along with aging. The dosing regimen in this study corresponded to a real life situation, but escitalopram doses up to 20 mg can been used. Also the use of tyramine-rich food can expose to adverse drug reactions in real terms. Smoking, which was forbidden in this study, could further complicate the implementation of drug treatment, since it is known to induce CYP1A2-mediated metabolism leading to reduced rasagiline exposure.

5. Conclusions

Although results from this study suggest no clinically significant interactions between escitalopram and rasagiline, many circumstances can complicate the therapy in patients with Parkinson's disease. This study demonstrates that these medications can be used together safely, but generalisations of the safety of this drug combination in diverse patient populations cannot be made due to the above discussed limitations. Nevertheless, the results of this study provide a solid and important foundation for future studies that address these limitations. Careful follow-up for excess monoaminergic effects is recommended when starting a concomitant rasagiline–escitalopram treatment.

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