Central nervous system effects of the interaction between risperidone (single dose) and the 5-HT₆ antagonist SB742457 (repeated doses) in healthy men

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Several lines of evidence suggest a possible role of 5-HT₆ receptor antagonists in dementia or cognitive dysfunction of schizophrenia. SB-742457 is a potent 5-HT₆ antagonist and has shown efficacy in different animal models of cognitive impairment. It is currently in development as a cognitive enhancer. Risperidone, commonly used to control agitation and psychotic features in both schizophrenia and Alzheimer's disease, is a D₂/5-HT_{2A} antagonist with low affinity for 5-HT₆ receptors and limited effects on cognitive parameters.

WHAT THIS STUDY ADDS

- As the combination of risperidone and SB-742457 may constitute a reasonable combination in cognitively impaired patients, pharmacodynamic interaction effects were investigated in this study. The only significant drug–drug interaction was a small increase of electroencephalogram (EEG) alpha and beta bands, which might suggest mild arousing activity of SB-742457 on the central nervous system-depressant effects of risperidone. The clinical relevance of these findings in patients remains to be established. Additionally, this study provided an extensive multidimensional pharmacodynamic profile of risperidone in healthy volunteers, showing that this antipsychotic suppresses motor performance (eye–hand coordination, finger tapping and postural stability), alertness, memory and neurophysiological functions (saccadic eye movements and EEG power spectrum).

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AIM

Several lines of evidence suggest a possible role of 5-HT₆ receptor antagonists in cognitive dysfunction of schizophrenia. Atypical antipsychotics, such as risperidone, are currently used in these disorders. Therefore, the pharmacological interactions between the 5-HT₆ antagonist SB-742457 and risperidone were investigated in the light of possible co-medication.

METHODS

A randomized, double-blind, two-way crossover design was used to study the interaction between multiple doses SB-742457 50 mg and a single dose risperidone 2 mg in 18 healthy subjects.

RESULTS

Treatment was well tolerated. The most common adverse event was somnolence in 83% during the combination vs. 50% of subjects after risperidone, 32% after placebo and 11% after SB-742457. Combination treatment produced a statistically significant increase in the maximum plasma concentration of risperidone and had no effect on SB-742457 pharmacokinetics. Risperidone decreased saccadic peak velocity, finger tapping, adaptive tracking, subjective alertness, delayed word recognition and body sway and increased electroencephalogram (EEG) theta power and prolactin. The only pharmacodynamic interaction of risperidone and SB-742457 was an increase of absolute EEG alpha (ratio = 1.25, 95% CI = 1.11, 1.40, *P* = 0.0004) and beta power (ratio = 1.14, 95% CI = 1.03, 1.27, *P* = 0.016). No significant effects of SB-742457 alone were found.

CONCLUSION

The pharmacokinetic interactions between SB-742457 and risperidone detected in this study were not clinically relevant. The increase in EEG alpha and beta power is incompatible with enhanced risperidone activity, but could point to mild arousing effects of the combination. Most pharmacodynamic changes of risperidone are consistent with previously reported data. The potential cognitive effects of SB-742457 remain to be established.

Introduction

Several recent lines of evidence have suggested a role of 5-hydroxytryptamine 6 (5-HT₆) receptors in cognitive and memory processes. Improvements in memory and other aspects of cognition have been reported using different 5-HT₆ antagonists, both in healthy animals and in animal models of cognitive impairment [1–7]. Several research groups have suggested that 5-HT₆ blockade may be involved in learning and memory via increased cholinergic transmission [5, 7–10] or modulation of dopaminergic transmission [11], but secondary changes in noradrenergic and glutamatergic neurotransmission may also be involved [12, 13]. Preliminary data from studies in patients with Alzheimer's disease (AD) suggest that the beneficial effects of treatments with 5-HT₆ receptor antagonists seen in animal models may translate into humans [14, 15].

In schizophrenia, the role of the 5-HT₆ receptor is less well defined. There is post-mortem evidence of reduced expression of the 5-HT₆ receptor in the hippocampus of schizophrenic patients [16]. Some of the most effective antipsychotic drugs partially bind to 5-HT₆ receptors, and 5-HT₆ receptors have been shown to be down-regulated by prolonged clozapine treatment in rats [17]. However, it is unknown if the reduced expression of 5-HT₆ receptors is due to the disease or chronic treatment.

At present, over a dozen selective 5-HT₆ antagonists are at various stages of development [14]. SB-742457 is a potent 5-HT₆ antagonist (pK_i = 9.6) with high affinity for human 5-HT_{2A} receptors (pK_i = 8.0; for structural formula see Figure 1). SB-742457 has shown efficacy in different animal models of cognitive impairment [14]. In humans, reports that SB-742457 is of clinical benefit in AD patients provided further evidence of the therapeutic potential of this approach [18, 19]. Repeated-dose studies in healthy subjects receiving daily 50 mg showed low occurrence of mild adverse events (AEs), mostly headache. At this dose, the exposure to SB-742457 is expected to deliver 5-HT₆ receptor occupancy of the central nervous system (CNS) above 90% (unpublished data). Clinical pharmacokinetic assessment showed that SB-742457 has a half-life of approximately 30 h, reaching steady state after 7 days with an accumulation ratio of about fourfold (unpublished data and [14]). Preclinical investigations showed that SB-742457 is a moderate inhibitor of CYP450 3A4.

Figure 1

Structural formula of SB-742457

For schizophrenia, SB-742457 would be considered for development as an add-on treatment to be used in combination with antipsychotic drugs (e.g. risperidone), known for their lack of clinical effect on cognition [20]. Risperidone is a dopamine 2 (D₂)/5-HT_{2A} antagonist with low affinity for 5-HT₆ receptors and limited effects on cognitive parameters [21] and is commonly used to control agitation and psychotic features. Therefore, the combination of risperidone and SB-742457 may constitute a reasonable combination in cognitively impaired patients. Risperidone is known to produce a series of CNS effects (such as sedation, increased theta band power of the electroencephalogram (EEG) spectra and increased prolactin concentrations) at doses of 1–2 mg in healthy volunteers [22]. It is primarily metabolized by CYP2D6, but CYP3A4 is also involved [23]. The main metabolite of risperidone is 9-hydroxyrisperidone, an active compound with a half-life of approximately 20 h [24]. The well-known profile of CNS effects may contribute to the cognitive impairment and the negative syndrome complex in some patients. As 5-HT₆ activity modulates dopaminergic transmission [11], it is hypothesized that some of the CNS effects due to neuroleptic agents are partially reversed by a 5-HT₆-antagonist like SB-742457. In this study the pharmacokinetic and pharmacodynamic effects of the interaction between SB-742457 and risperidone and of SB-742457 and risperidone alone were investigated in healthy volunteers. In this early stage of development of SB-742457, the pharmacodynamic effects had not been examined in humans, and its effects on risperidone could not be accurately predicted. Therefore, a multimodal test battery was used repeatedly, consisting of validated neurophysiological and neuropsychological tests. These tests have no direct bearing on schizophrenia and they only partly reflect the negative cognitive and behavioural effects of this condition (and the positive psychotic effects even less). However the battery accurately covers most drug-responsive CNS-functional domains, and therefore had a large chance of demonstrating pharmacodynamic changes induced by risperidone or SB-742457 alone, or the effects of their combination.

Methods

Volunteers

Twenty-four healthy male volunteers aged between 18 and 38 years with a bodyweight above 50 kg and a body mass index between 18.5–29.9 kg m⁻² were recruited for the study, with the aim of completing all treatments in at least 18 subjects. Subjects were considered 'healthy' by a responsible study physician, when no clinically significant abnormalities were identified on the medical or laboratory evaluation (haematology, biochemistry, virology, urinalysis and urine drug screen), blood pressure and heart rate or 12-lead ECG before the study starts medical. Exclusion criteria included the use of agents known to affect CNS func-

tions (including drug or alcohol use), smoking more than five cigarettes a day and unable to refrain from smoking during the stay in the research unit. The Ethics Review Board of the Leiden University Medical Centre approved the study protocol. Written informed consent was obtained from all volunteers following a written and oral explanation.

Study design

This was a randomized, double-blind, double-dummy placebo controlled crossover study, consisting of two 11-day multiple dosing periods for either SB-742457 50 mg or placebo (see Figure 2). On days 8 and 9 of each period, a single dose of risperidone 2 mg or placebo was administered in a balanced randomized crossover fashion. In this way, the effects of risperidone (either alone or with SB-742457) could be examined after acute administration (on day 8 or on day 9 after placebo treatment on the preceding day). There was at least 1 week washout between the two multiple-dose periods. Subjects received SB-742457 from day 1 until day 11. They visited the research centre in the morning on days 1 to 7 and days 11 to 14 and remained in house from the morning of day 8 until the morning of day 10. Both SB-742457 (capsule) and risperidone (tablet) or their matching placebos were administered once daily with a glass of water.

Before administration of the study medication all participants were instructed to remain fasted. Smoking was not allowed during the study days, volunteers refrained from alcohol and xanthine-containing foods or beverages from 24 h before each study period until day 12, and grapefruit products were not allowed from 14 days prior to the study until the end of the study.

Pharmacokinetics

Blood samples (approximately 3 ml) were obtained pre-dose on days 6 and 7 (for SB-742457 measurements only), and days 10, 11 and 12 (for SB-742457, risperidone and 9-hydroxyrisperidone measurements). On days 8 and 9, blood samples were taken for SB-742457, risperidone and 9-hydroxyrisperidone at baseline and 45, 80, 140, 190, 235, 345 min and 8 and 12 h after administration of both drugs.

Plasma samples were analysed for SB-742457 by Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Ware, UK, using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) analysis. The lower limit of quantification (LLQ) for SB-742457 was 1 ng ml⁻¹, using a 50 µl aliquot of EDTA plasma with a higher limit of quantification (HLQ) of 5000 ng ml⁻¹. Plasma samples were analysed for risperidone and 9-hydroxyrisperidone by York Bioanalytical Solutions, York, UK, using a validated analytical method based on protein precipitation, followed by HPLC-MS/MS analysis. The LLQ for both risperidone and 9-hydroxyrisperidone was 0.1 ng ml⁻¹, using a 50 µl aliquot of human plasma with a HLQ of 100 ng ml⁻¹ [25].

Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analysed with each batch of samples against separately prepared calibration standards. For the analysis to be considered acceptable, no more than one-third of the QC results deviated from the nominal concentration by more than 15%, and at least 50% of the results from each QC concentration were within 15% of nominal. The applicable analytical runs met all predefined run acceptance criteria.

Figure 2

Scheme of study periods 1 and 2, which were similar and separated by at least 1 week washout

Pharmacodynamics

On days 8 and 9, a pharmacodynamic test battery was performed twice at baseline and 45, 80, 140, 190, 235, 295, 345 min and 8 and 12 h after administration of both drugs. The battery takes about 20 min and consists of the pharmacodynamic assessments described below, which were performed in a quiet room with subdued light with one volunteer per room. No more than 1 week before the start of the study, the volunteers were familiarized with the test procedures during a training session.

Pharmacoelectroencephalography

Pharmacoelectroencephalography (Pharmacoe-EEG) was performed as a general measure of CNS activity [26]. The literature suggests that antipsychotics produce distinct profiles of EEG changes [27, 28]. EEG recordings were made using silver chloride electrodes, fixed with collodion at Fz, Cz, Pz and Oz (international 10/20 system), as previously described [29]. Fast Fourier transform analysis was performed to obtain the sum of amplitudes in the delta- (0.5–3.5 Hz), theta- (3.5–7.5 Hz), alpha- (7.5–11.5 Hz) and beta- (11.5–30 Hz) frequency ranges. The square root of the total power (μV) was analysed. The duration of one EEG recording was 64 s (i.e. eight blocks of 8 s).

Saccadic and smooth pursuit eye movements

Eye movements were recorded as previously described [30, 31] and have shown effects with many different CNS active compounds, including GABA-ergic [22, 32, 33], serotonergic [34], noradrenergic [35–37] and dopaminergic agents [22, 29]. For saccadic eye movements, the average values of latency (reaction time), saccadic peak velocity and inaccuracy of all artifact free saccades were calculated. The average percentage of smooth pursuit for all stimulus frequencies was used.

Adaptive tracking

The adaptive tracking test has proved to be useful for measurement of the CNS effects of alcohol [38], various psychoactive drugs [26, 39] and sleep deprivation [30, 38]. It measures visuo-motor coordination and vigilance and was performed as originally described by Borland [39], using customized equipment and software (Hobbs, 2000, Hertfordshire, UK). The average performance scores over a 3-min period were used for analysis, as described previously [29].

Body sway

Changes in body sway have been seen for many different CNS active drugs, including GABA-ergic compounds [32, 33], dopaminergic agents [29] and tetrahydrocannabinol (THC) [40]. The body sway allows measurement of body movements in a single plane, providing a measure of postural stability. Body sway was measured with an apparatus similar to the Wright ataxiometer [28]. With a string

attached to the waist, all body movements over a period of 2 min were integrated and expressed as millimetre sway on a digital display. Measurements of body sway were made in the sagittal planes. All assessments were made with the eyes closed, standing with feet 10 cm apart wearing comfortable low-heeled shoes. The total amount of movement was used for statistical analysis.

Subjective assessments

Visual analogue scales (VAS) consist of 100 mm line segments. Subjects put a mark on a point on the line that best represents their subjective state corresponding to the condition tested. The result is a distance (mm) calculated from the mark on the line.

Subjective effects were quantified using a Dutch translation of the 16 VAS originally described by Norris [41]. They have been used previously to quantify subjective effects of a variety of agents, including sedative [32, 33], dopaminergic drugs [22, 29], scopolamine (Centre for Human Drug Research data on file) and THC [40]. From these measurements, three factors are derived as described by Bond and Lader [42], corresponding to alertness, mood and calmness [32, 33, 43]. A lower score on these scales indicates sedation, excitation and decrease in mood (or contentedness) respectively.

A translated version of the Bowdle psychotomimetic VAS [44] showed effects of THC [40], zolpidem [43] and scopolamine (Centre for Human Drug Research data on file). The lowest extreme is '0', signifying complete absence of the state (which is the case under normal circumstances), the highest the 'most extreme state imaginable'. The VAS scores were performed electronically using custom-written and validated E-prime scripts (<http://www.pstnet.com/eprime.cfm>).

Finger tapping

The finger tapping test was adapted from the Halstead Reitan Test Battery [45]. The test evaluates motor activation and fluency. Speed of finger tapping was measured for the index finger of the dominant hand; a session contained five performances of 10 s. The volunteer was instructed to tap as quickly as possible on the space bar of a keyboard. The mean tapping rate and the standard deviations are used for statistical analysis.

Visual Verbal Learning Test

Memory includes many different components of learning behaviour, such as acquisition, consolidation, storage and retrieval. The Visual Verbal Learning Test (VVL) contains three different subtests that cover most of the scope of learning behaviour, i.e. immediate and delayed word recall and a delayed word recognition [46]. This test is a modified version of the auditory verbal learning test [47] in which 30 words are shown. This test is known to be sensitive to the CNS effects of various compounds such as benzodiazepines [32], cannabinoids [40] and scopolamine [48]. The

outcome measures for the immediate and delayed word recall were the average and the maximum number of correct responses. For the delayed word recognition, the number of correct items and mean response time for correct responses were recorded.

Plasma prolactin concentrations

Prolactin increase induced by antipsychotics is closely related to D₂-receptor antagonism [22]. Prolactin concentrations were measured predose and at 30, 45, 60, 80, 140, 190, 235, 345 min and 8 h after administration of both drugs as described previously. For this purpose, blood samples were collected in plain 3-ml tubes and kept at room temperature for 30 to 45 min. Serum was separated by refrigerated centrifugation (2000 *g* at 4°C for 10 min) within 1 h of collection and transferred to polypropylene tubes. Serum specimens were stored at approximately –20°C until analysis. The hormone assays were performed by the Central Clinical Chemistry Laboratory of the Leiden University Medical Center and were performed by electrochemiluminescence immunoassay on a Modular Analytics E170 (Elecys module) immunoassay analyser. The assay had a LLQ of 0.047 µg l⁻¹, an intra-assay precision (expressed as coefficient of variation) of 1.81–1.90% and inter-assay precision of 2.39–2.64%.

Statistical analysis

Pharmacokinetic analysis Pharmacokinetic analyses of plasma SB-742457, risperidone, 9-hydroxyrisperidone and total risperidone active moiety concentration–time data were conducted using non-compartmental methods.

Main pharmacokinetic endpoints were maximum observed concentration ($C_{\max}$) and area under the plasma concentration–time curve up to last time point [AUC(0,*t*)] and extrapolated to infinity [AUC(0,∞)] of risperidone and 9-hydroxy-risperidone, while $C_{\max}$ and AUC over the dosing interval were evaluated for SB-742457. Plasma concentration–time data were evaluated by standard non-compartmental analysis using WinNonlin Professional Version.

The study sample size was based on feasibility. A variability estimate of 0.32 for AUC(0,∞) of risperidone was taken from published results for a risperidone/venlafaxine interaction study [49]. With such variability, it was estimated that with 16 evaluable subjects (of the 20 recruited) completing the study, the lower and upper limits of the 90% confidence interval (CI) for the ratio of geometric means (ratio of SB-742457 + risperidone and placebo + risperidone) would have been within 20.9% of the point estimate. In practice, assuming a true ratio of 1, this precision would have lead to a 90% CI of 0.83 to 1.21.

Following log transformation, total risperidone (active moiety) AUC(0,*t*), AUC(0,∞) and $C_{\max}$ and SB-742457 AUC(0,*t*) and $C_{\max}$ were analysed using a mixed effects model with session, day, regimen and regimen × day as fixed effects and subject as a random effect. Point esti-

mates and corresponding 90% CIs for the differences between risperidone in presence of SB-742457 compared with risperidone in presence of placebo were obtained using the residual variance from ANOVA. These data were then exponentially back-transformed to give estimates of the ratios of geometric means and 90% CIs. Lack of drug interaction between SB-742457 and risperidone would have been demonstrated if the 90% CI was completely contained within 0.80, 1.25.

Pharmacodynamic analysis This analysis was exploratory and the formal power estimate was performed according to pharmacokinetic criteria (see above). However, past experience at the study site and published information on EEGs indicated that pharmacodynamic signals could be seen using 8–12 subjects. All endpoints were analysed using an ANOVA model, which was fitted using PROC MIXED in SAS. For VVLT and prolactin endpoints, the model included session, day, regimen, day × regimen, and, when available, baseline as fixed effect terms and subjects as a random effect term. For all other endpoints, the model included session, day, regimen, time, day × regimen, time × regimen and day × time × regimen as fixed effect terms and subjects and subject × session × day as random effect terms.

The following Least Square Means differences were computed to investigate the related treatment effect:

- *Risperidone effects*: placebo SB-742457 + risperidone (day 9) vs. placebo SB-742457 + placebo risperidone (day 8).
- *SB-742457 effects*: SB-742457 + placebo risperidone (day 8) vs. placebo SB-742457 + placebo risperidone (day 8).
- *Effects of SB-742457 co-administration on risperidone effects*: SB-742457 + risperidone (days 8 and 9) vs. placebo SB-742457 + risperidone (days 8 and 9).

No correction for multiple comparisons among the various endpoints was performed as this analysis was considered exploratory.

Results

Study population

Twenty-four volunteers were included in the study and six volunteers were withdrawn from the study, resulting in 18 completers. Three subjects withdrew for non drug-related AEs, one for protocol violation, one for personal reasons and one because of a rash (during placebo, see below). Volunteers had a mean (min–max) age of 24.8 (18–38) years, were healthy and took no relevant concomitant medications.

Tolerability

No clinically significant changes were observed for vital signs, respiratory functions, physical examination or

Table 1

Adverse events (AEs) reported on days 8 and 9 after SB-742457, risperidone, the combination of SB-742457 and risperidone and placebo

Most frequent AEs (at least two events)	SB-742457 n = 19 n (%)	Risperidone n = 20 n (%)	SB-742457 + risperidone n = 18 n (%)	Placebo n = 19 n (%)
Somnolence	2 (11)	10 (50)	15 (83)	3 (16)
Headache	1 (5)	2 (10)	2 (11)	3 (16)
Dizziness	0 (0)	8 (40)	4 (22)	2 (9)
Disturbance in attention	1 (5)	3 (15)	1 (6)	0 (0)
Nausea	0 (0)	2 (10)	0 (0)	2 (9)
Fatigue	2 (11)	5 (25)	3 (17)	2 (9)

laboratory parameters. There were no serious AEs in this trial. The reported AEs are shown in Table 1. The AEs coded as 'possibly related to the study medication' were of mild to moderate intensity and resolved spontaneously. The most frequently reported AE, irrespective of causality, was somnolence. More subjects experienced somnolence following SB-742457 in combination with risperidone (83%) compared with risperidone alone (50%). On days 8 and 9, somnolence was reported by three subjects (16%) receiving placebo and by two (11%) receiving SB-742457 alone. One subject, after exposure to placebo SB-742457 for 5 days, was withdrawn from the study because of the occurrence of a papular rash on chest, back, hands and arms. It was not associated with any out-of-range liver enzyme or other laboratory values and resolved without treatment after 11 days. Overall, SB-742457 50 mg was generally well tolerated when administered orally once daily for 11 days, and also when administered at steady state in combination with a single 2-mg oral dose of risperidone.

Pharmacokinetic results

The peak plasma concentration of risperidone was 15 ng ml⁻¹ at 2.3–2.7 h with an elimination half-life of ~4 h. Following oral co-administration of SB-742457 (50 mg) at steady state with a single dose of risperidone, mean increases in C_{max} were estimated for total risperidone active moiety (15%), risperidone (19%) and 9-hydroxyrisperidone (6%) compared with placebo (see Figure 3). The ratio (and 90% CIs) for C_{max} were 1.19 (1.04, 1.35) for risperidone, 1.15 (1.02, 1.28) for the total risperidone active moiety and 1.06 (0.96, 1.17) for 9-hydroxyrisperidone. No substantial increases in AUC were found. Overall, co-administration of risperidone with steady state SB-742457 did not alter the pharmacokinetics of SB-742457 compared with placebo.

Pharmacodynamic results

Risperidone effects Risperidone caused a considerable number of effects on subjective, neurophysiological and performance parameters. Compared with placebo, risperidone substantially decreased saccadic peak velocity, finger tapping, adaptive tracking, delayed word recognition and

Figure 3

Mean plasma concentrations (standard errors) of risperidone active moiety in the 18 healthy volunteers who completed the study. Risperidone + SB742457 (—●—); Risperidone + placebo (---○---).

body sway, while subjective alertness and contentedness deteriorated (as assessed by the VAS Bond & Lader) and increased EEG theta power and prolactin concentrations (differences, 95% CI, and *P* values are shown in Table 2).

SB-742457 effects When measured after single doses of risperidone or placebo on both days 8 and 9, no statistically significant differences were detected on any of the pharmacodynamic parameters between subjects daily exposed to 2 weeks of placebo and SB-742457 (data not shown).

Effects of SB-742457 co-administration on risperidone effects A single dose of risperidone in subjects during multiple daily doses of SB-742457 produced significant increases of absolute alpha Pz-Oz and beta Pz-Oz power

Table 2

Pharmacodynamic crossover effects of risperidone vs. placebo risperidone (single dose) in subjects exposed daily to placebo SB-742457 (multiple dose)

Parameter	Placebo SB-742457 + risperidone (day 9)*	Placebo SB-742457 + placebo risperidone (day 8)*	Difference (95% CI)	P value
Saccadic eye movement				
Peak velocity (deg s ⁻¹)	405.1	475.8	-70.7 (-91.3, -50.1)	<0.0001
Smooth pursuit eye movement (%)	47.5	52.7	-5.2 (-10.5, 0.1)	0.0562
Finger tapping				
Average (taps 10 s ⁻¹)	58.0	63.2	-5.2 (-7.8, -2.6)	0.0002
Adaptive tracking				
Average (%)	17.6	22.4	-4.8 (-7.1, -2.5)	0.0001
VAS† – Bond & Lader				
Alertness (mm)	55.7	44.0	11.8 (2.7, 20.8)	0.0124
Contentedness (mm)	43.3	35.5	7.8 (1.4, 14.2)	0.0178
Visual Verbal Learning Test				
Average reaction time correct recognitions (ms)	840.12	945.89	-105.77 (-203.95, -7.59)	0.0353
Body sway (mm)	372.8	301.0	ratio1.24 (1.07, 1.44)	0.0058
Electroencephalogram‡				
Absolute power theta Fz-Cz (µV)	2.56	2.19	ratio1.17 (1.03, 1.33)	0.0175
Absolute power theta Pz-Oz (µV)	2.72	2.34	ratio1.16 (1.02, 1.33)	0.0299
Prolactin serum concentration				
AUC (0.5–8) (ng ml ⁻¹ h)	179.88	41.30	4.36 (3.65, 5.19)	<0.0001
C _{max} (ng ml ⁻¹)	53.12	8.19	6.48 (5.25, 8.01)	<0.0001

*LSM, Least Square Means; †VAS, Visual Analogue Scale; ‡Only (almost) statistically significant values are reported; non-significant values are reported online.

compared with placebo SB-742457, while no difference was observed in other endpoints (i.e. saccadic peak velocity, smooth pursuit eye movement, finger tapping, adaptive tracking, VAS Bond & Lader, VVLT, body sway, prolactin serum concentrations and other EEG measures; all values are shown online in Table 3).

Discussion

The 5-HT₆-antagonist SB-742457 is under development as a possible treatment for the cognitive symptoms in AD and possibly in schizophrenia. This study was set up to evaluate the pharmacokinetic and CNS interactions between SB-742457 and risperidone, as this 5-HT₆ antagonist may be used as an add-on therapy in combination with atypical antipsychotics, which may contribute to reduce cognitive impairment in some schizophrenic patients.

The results indicate that co-administration of SB-742457 with risperidone did not alter AUC (all AUC 90% CIs were contained within the 0.80, 1.25 equivalence interval). There was a minor increase in peak exposure (C_{max}) of the total risperidone active moiety (15%), which was caused by an elevation of risperidone concentrations (19%) without a change of the active metabolite 9-hydroxyrisperidone. This could be related to an inhibition by SB-742457 of CYP450 3A4, which is one of the cytochrome P450 systems involved in the metabolism of

risperidone [23]. Although the differences in C_{max} were statistically significant for risperidone and the active moiety, the extent of the increase was very modest and, taking into consideration the inter-subject variability, does not appear to be of any clinical relevance.

Risperidone produced its expected AE profile [50], while SB-742457 50 mg was well tolerated when administered orally once daily for 11 days either alone or in combination with a single 2-mg oral dose of risperidone. The most frequently reported AE, irrespective of causality, was somnolence, which occurred in a greater proportion of subjects in the presence of risperidone (with or without active SB-742457) than with placebo. However, the numbers of events were too small to draw strong conclusions.

A battery of quantitative CNS tests was used to assess the pharmacodynamic interaction between risperidone and SB-742457 in healthy volunteers. These tests were chosen for their sensitivity to classic antipsychotic agents as well as to a wide range of other CNS active drugs. Repeated daily exposure to 50-mg SB-742457 did not produce any detectable effects on any of the pharmacodynamic CNS tests when compared with placebo. Additionally, this study yielded an extensive multidimensional pharmacodynamic profile of risperidone in healthy volunteers, showing that this antipsychotic suppresses motor performance (eye–hand coordination, finger tapping and postural stability), alertness, memory

and neurophysiological functions (saccadic eye movements and EEG power spectrum). Several of these effects confirm the effects of risperidone found in previous studies in healthy volunteers: decreased behavioural and cognitive performance, increased theta band power of the EEG spectra, decreased saccadic peak velocity and increased prolactin concentrations [50–53]. Although the observed increase in EEG theta power agrees with the effects described by De Visser *et al.* [22], a decrease in EEG alpha and an increase in delta power could also have been expected. When risperidone was administered to subjects exposed to daily SB-742457, the effects were generally similar to those exposed to daily placebo, except that SB-742457 combined with risperidone caused a significant increase of EEG alpha and beta power, compared with risperidone alone. Although it is difficult to assign functional significance to EEG changes, increases in EEG alpha or beta power are not typically because of sedation and have been associated with internally directed attention and increased mental load [54]. This result could be interpreted as mild subclinical arousing activity of SB-742457 in the presence of risperidone. Although this finding clearly does not constitute definitive proof, this could be considered as an indication for modulation of dopaminergic hypofunctionality by 5-HT₆ antagonism.

The effects were too limited to be certain of pharmacological interactions between SB-742457 and risperidone. This could be related to the unknown sensitivity of this study to detect subtle pharmacodynamic effects, because the study was powered on the pharmacokinetic outcomes. However, in other studies with similar population sizes, a similar CNS battery detected mild enhancing effects of other serotonergic agents with diverse pharmacological characteristics and for various receptor subtypes [34, 55, 56]. It is also possible that the administered dose of SB-742457 did not have any beneficial pharmacodynamic effects by itself, because of ceiling effects in healthy subjects, or functional compensation of 5-HT₆ receptor inhibition in this population.

In conclusion, there was no clinically relevant pharmacokinetic drug–drug interaction between SB-742457 50 mg and risperidone 2 mg. Repeated dosing with SB-742457 did not increase AEs or cause any pharmacodynamic effects in healthy young males, whereas a single dose of risperidone produced the expected profile of (side) effects. In general, the combination of SB-742457 and risperidone did not affect CNS function more than risperidone alone. The only statistically significant pharmacodynamic interaction was an increase of EEG alpha and beta bands, suggesting a mild arousing activity of SB-742457 on some CNS-depressive effects caused by risperidone, possibly mediated by 5-HT₆ receptors. The pharmacological or functional significance of these findings remains to be determined, although these interactions might indicate that SB-742457 penetrates the blood–brain barrier and modifies some effects of an antipsychotic drug.

Competing Interests

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