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Concomitant blockade of 5-HT_{1A} receptor and 5-HT transporter: Use of the Hunter Serotonin Toxicity Criteria in a clinical pharmacology study

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Abstract

There is a potential risk that 5-HT_{1A} receptor blockade combined with blockade of the 5-HT transporter by an SSRI may cause a toxic increase in 5-HT within the synapse, sparking concern for 'serotonin syndrome', a rare but potentially life threatening condition. We evaluated the safety and pharmacodynamics of the combination of the 5-HT_{1A} antagonist lecozotan and the SSRI citalopram in a well-controlled Clinical Pharmacology Unit setting using the Hunter Serotonin Toxicity Criteria (HSTC), a set of validated decision rules featuring neurological and body temperature measurements, to detect any clinically relevant serotonin toxicity. Forty-three young healthy male subjects were randomized, to 2 parallel double-blind treatment groups following a 10-day citalopram 40 mg run-in period: citalopram 40 mg/lecozotan 10 mg or citalopram 40 mg/placebo for 9 days. Overall, the combined administration of active drugs was well tolerated, however, one subject experienced moderate hyperreflexia, tremor of the hands, and sweating of hands and feet after 3 days of combined treatment. The event prompted treatment withdrawal and was regarded as mild serotonin toxicity, as per the HSTC. The onset of the event was around the time of peak plasma concentrations (t_{max}) of both lecozotan and citalopram, and its time course corresponds to the well-defined PK profile of lecozotan. No evidence of a PK interaction was detected trough lecozotan and citalopram plasma

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concentrations analysis. The utility of the HSTC in detecting the non-discrete group of symptoms commonly referred to as "serotonin toxicity" was demonstrated in this clinical pharmacology study combining two 5-HT agents in a clinically controlled setting.

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1. Introduction

It is a recognized concern that the combination of two drugs acting on serotonin (5-HT) may cause an increase in 5-HT within the synapse, with the risk of the occurrence of the rare but potentially life-threatening condition 'serotonin syndrome'. This is a seldom diagnosed condition identified as being a non-idiosyncratic reaction primarily reported after selective serotonin reuptake inhibitor (SSRI) overdose or combined SSRI/monoamine oxidase inhibitors (Boyer and Shannon, 2005; Isbister et al., 2007). Prior to the onset of the more serious 'serotonin syndrome', serotonin toxicity (ST) can occur as a result of any increase in intra-synaptic serotonin levels, and the severity of associated symptoms spans a spectrum of toxicity that correlates with the serotonin concentration in the synaptic cleft. The major clinical features consist of neuromuscular hyperactivity, autonomic hyperactivity and altered mental status, which may present abruptly and progress rapidly. The awareness of ST is essential for both avoiding lethal drug–drug interactions and recognizing the clinical situation when it occurs so that appropriate management, including pharmacological treatment, can be promptly initiated. The syndrome is reported as occurring in approximately 60% of patients within 6 h after initial use of medication, an overdose, or changes in dosing and occurs in approximately 15% of people overdosing on SSRIs (Isbister et al., 2004). Mild cases tend to resolve within 24 to 72 h with conservative therapy and the removal of the causative drugs, with the majority of these cases not requiring hospitalization. Hence the importance of early recognition and medical supervision of ST as described by Gillman (1999).

The Hunter Serotonin Toxicity Criteria (HSTC) is a set of validated decision rules that includes neurological examination and body temperature measurements, used to detect any clinically relevant ST. The HSTC was developed as a practical approach to diagnosis and treatment of ST. The set of criteria evolved from a retrospective analysis of overdose cases presenting to a hospital emergency room following known ingestion of serotonergic agents. It has been shown to be highly sensitive to and specific for diagnosing ST in a clinical setting, when compared to using other diagnostic tools such as Sternbach's Criteria (Dunkley et al., 2003). Diagnosis with the HSTC requires one of the following features or group of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature above 38 °C, and ocular or inducible clonus as shown in the flow diagram in Fig. 1 (Isbister et al., 2007).

The present study reports the novel use of this scale in a clinical pharmacology study. The authors used the HSTC to evaluate an *a priori* risk of ST in a prospective manner in healthy male subjects.

Lecozotan is a selective, full serotonin-1A (5-HT_{1A}) antagonist that was investigated by Wyeth Research (now

Pfizer Inc.; Schechter et al., 2005). For the past decade 5-HT_{1A} antagonists such as lecozotan have been evaluated for their utility in the treatment of cognitive dysfunction, such as that seen in Alzheimer's disease (Childers et al., 2007). Because 5-HT_{1A} presynaptic somatodendritic receptors (autoreceptors) are involved in the inhibition of 5-HT release, 5-HT_{1A} blockade with lecozotan combined with blockade of the 5-HT transporter by an SSRI could potentially increase the risk of ST, ultimately leading to the so-called 'serotonin syndrome'. Beyond the theoretical safety risk, a combined 5-HT_{1A}/SSRI approach has also been proposed to both accelerate and augment the effects of SSRIs in depressed patients. Indeed, in a review of studies, where SSRIs and pindolol (a mixed beta-adrenergic antagonist with antagonist properties at the 5-HT_{1A} receptor) were combined, the data are encouraging from a safety point of view, where ST was not observed (Leuchter et al., 2008). In addition, buspirone, which acts as a partial agonist at the 5-HT_{1A} receptor, has been used for many years, especially in the United States, as an augmenter of SSRIs for antidepressant response without incident (Segrave and Nathan, 2005). However, results should be viewed with caution as there is the possibility that clinically depressed patients may show a more favorable safety profile compared to other categories of patients or healthy subjects as endogenous levels of intrasynaptic 5-HT are known to be characteristically low.

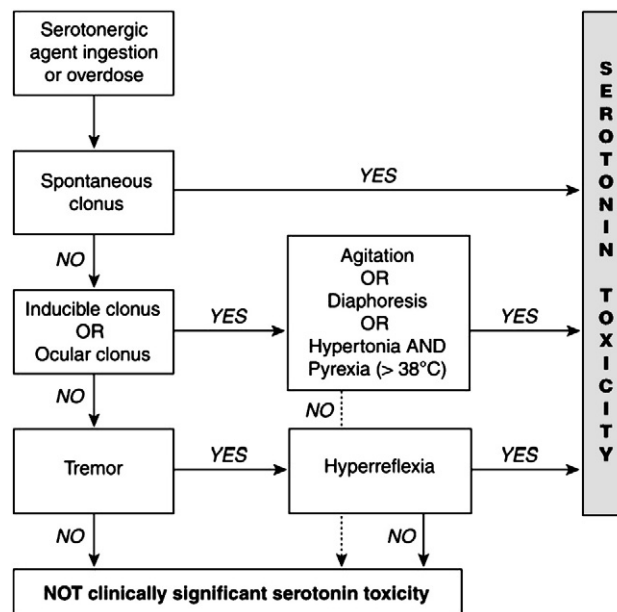


Figure 1 Flow diagram based on the Hunter Serotonin Toxicity.

Isbister GK et al. Serotonin toxicity: a practical approach to diagnosis and treatment. MJA 2007; 187: 361–365. ©Copyright 2007. The Medical Journal of Australia – reproduced with permission.

This clinical pharmacology study in healthy young adult subjects was designed primarily to evaluate the safety and tolerability of combined lecozotan and an SSRI in a well-controlled environment where ST could easily be recognized and managed by experienced and trained physicians. Citalopram was selected as the ideal SSRI probe for this study, because it is neither the source nor the cause of clinically relevant CYP-mediated drug interactions and has therefore a low risk for a pharmacokinetic interaction with lecozotan, for which clinically relevant CYP-mediated interactions are possible (Brosen and Naranjo, 2001). In addition, it is considered the first-choice treatment for mood disorders in elderly subjects and patients with AD (Brosen and Naranjo, 2001; Gutierrez and Abramowitz, 2000). Interestingly, a review of safety data from a clinical trial in healthy subjects combining citalopram with pindolol does not suggest that occurrence of 'serotonin syndrome' should be a problem with this particular combination (Segrave et al., 2006). Furthermore, of all the commonly prescribed SSRIs few sporadic case reports of 'serotonin syndrome' have been reported in association with ingestion of citalopram in overdose (Mason et al., 2000).

The lecozotan 10-mg dose selected has been shown to be safe and well tolerated in healthy subjects and is associated with detectable brain receptor occupancy (in the temporal cortex) of 56–72% based on positron emission tomography data generated in elderly healthy subjects and subjects with AD after single dose administration of an immediate release formulation (Patat et al., 2009; Raje et al., 2008).

The objectives of this study were to evaluate the safety, tolerability, and pharmacodynamics of combined treatment with the SSRI antidepressant citalopram and the 5-HT_{1A} receptor antagonist, lecozotan, in healthy volunteers under safely controlled conditions. Importantly, the focus of the safety evaluations to be conducted during the study was the HSTC, a validated tool relying on neurologic examination and body temperature measurements completed on a daily basis at multiple time points during the entire treatment duration and used to proactively detect the possible occurrence of ST.

2. Experimental procedures

This was a single-center, double-blind, randomized, parallel-group, inpatient study performed in healthy young men that was conducted at Icon Development Solutions (Manchester, England). The study protocol, investigator's brochure and informed consent form were reviewed and approved by the Manchester Independent Research Ethics Committee, United Kingdom, and conducted in accordance with the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

2.1. Subjects

Forty-three healthy male subjects aged 19 to 49 years, with a mean age of 29 years, were enrolled in the study. Inclusion criteria required subjects to be healthy (determined by the investigator on the basis of medical history, physical examination, psychiatric examination (performed by a psychiatrist), clinical laboratory test results, vital sign measurements, and 12-lead electrocardiogram (ECG)); to have a body mass index (BMI) of 18–30 kg/m² and a body weight of at least 50 kg; subjects could not use prescribed or non-prescribed drugs 1 month prior to and during the study, nor could

they consume excess alcohol (exceeding 50 g/day) or more than 3 cups of coffee (>300 mg/day) per day, in addition, they had to be non-smokers or smokers of fewer than 10 cigarettes per day. Exclusion criteria included any condition detected at screening that could have interfered with or biased the neurological examinations performed during the study, such as essential tremor.

The majority of enrolled subjects were Caucasian (34, 79%). Twenty-one (21) were randomly assigned to the administration of placebo and citalopram 40 mg and 22 were randomly assigned to lecozotan 10 mg and citalopram 40 mg. Of the 43 enrolled subjects, 7 (16.3%) were discontinued from the study. One (1) subject discontinued during the citalopram alone phase at the request of the investigator, for aggressive behavior. He also had a high temperature and excessive sweating that could have been caused by lack of tolerability to citalopram. The remaining 6 subjects to discontinue were due to adverse events (AEs), 4 subjects discontinued during the citalopram phase alone (before combined treatment) and 2 discontinued during the citalopram and lecozotan phase. As a result, 17 subjects received placebo and citalopram 40 mg and 21 subjects received lecozotan 10 mg and citalopram 40 mg.

2.2. Drug administration

A dose-titration approach (20 mg for the first two days followed by 40 mg from day 3 to day 19) was used with citalopram (Celexa®), which was administered in an open-label manner for a total of 19 days; alone for 10 days then combined on days 11–19 with a double-blind sustained release formulation of lecozotan or placebo (1:1). The study consisted of 2 parallel treatment groups: (A) administration of lecozotan 10 mg and citalopram 40 mg or (B) administration of placebo and citalopram 40 mg. Subjects were randomly assigned to 1 of these 2 treatment arms and evaluated in staggered cohorts of no more than 8 subjects (50% with placebo) so that subjects exhibiting a lack of tolerability could be managed appropriately. The dosing regimens of the current study are illustrated in Fig. 2.

2.3. Safety evaluations

Safety was assessed through spontaneous reporting of AEs, supine blood pressure and heart rate, continuous tympanic temperature monitoring, 12-lead ECG, routine laboratory tests, the HSTC, and a withdrawal questionnaire. The HSTC evaluation included a neurological examination and measure of body temperature on study day -1 and then every day at 4 h after dosing (approximate T_{max}). The Profile of Mood States (POMS), a 6-dimension questionnaire evaluating affect or mood including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia and confusion-bewilderment, was completed on days -1, 11 (predose), 12, 19 and 21 before test article administration. If any subject experienced any of the 5 criteria in the HSTC decision rules, the finding was reported as an AE and drug administration stopped. Subjects should then have been carefully monitored and rescue medication considered. If this happened for more than one subject, early termination of the study would have been considered.

2.4. Pharmacodynamics

Cortisol and prolactin were collected on study days 10 (steady state citalopram), 11 and 19, before (predose) and after test article administration at hours 2, 4, 6, 8, 10, 12 and 24. The PD samples were analyzed for prolactin and cortisol by a validated immunoassay using lanthanide fluoroimmunoassay reagents (DELFI). The samples were analyzed at Icon Development Solutions, Manchester, UK.

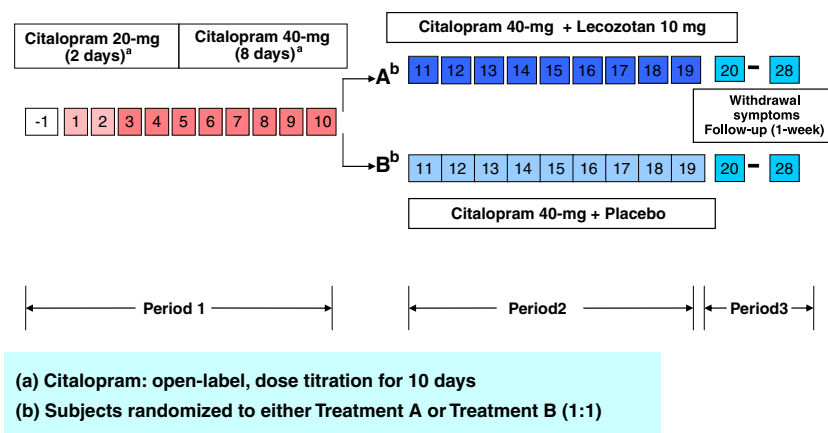


Figure 2 Illustration of dosing regimens.

2.5. Pharmacokinetics

Trough blood samples (6 mL) for determination of lecozotan and citalopram were obtained on days 9, 10, 12, 13, 18, 19 and 21. Plasma samples were assayed for lecozotan using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) analytical method. Lecozotan assay was linear over a range of 0.5 to 500 ng/mL. Plasma samples were assayed for citalopram using a validated LC/MS/MS assay. Citalopram was linear over the range of 0.5 to 80 ng/mL. Plasma S- and R-citalopram were assayed using a validated LC/MS/MS method linear over the range of 0.2000 to 30.00 ng/mL for both (R)-citalopram and (S)-citalopram. No formal noncompartmental PK analysis was performed. Trough concentrations were reported and descriptive statistics were performed for all analytes.

2.6. Data analysis

Administration of lecozotan and citalopram in combination to 20 subjects provided a 95% probability of observing at least 1 occurrence of ST (based on HSTC decision rules) assuming a true incidence rate of 15%, as reported in cases of SSRI overdose or with the combination of moclobemide and an SSRI (Gillman, 1999).

The primary endpoint was the proportion of subjects experiencing ST based on the HSTC decision rules over days 11 to 19. The primary analysis was the comparison of the proportions of subjects with ST (i.e., at least 1 Hunter criterion) among treatment groups. Estimates of proportions and the corresponding 2-sided exact 95% confidence intervals (CIs) for each treatment group were calculated. Safety and PD data were summarized for treatments A and B over 3 treatment periods: citalopram administration (days 1 to 10); citalopram/placebo or citalopram/lecozotan administration (days 11 to 19); and withdrawal phase (days 20 to 28). Safety (e.g., POMS scale) and PD parameters (e.g., tympanic temperature, prolactin, and cortisol) were compared among the treatments by using an analysis of covariance with baseline as a covariate and treatment as a factor separately at each time point. For prolactin and cortisol, the primary statistical analysis (days 11 to 19) was conducted on time-matched baseline-adjusted values. The sample collected on day 10 was subtracted from the measurement (change from baseline) collected on day 11 at the same nominal clock time after treatment. For the POMS analysis, measurement on day 11 before dose administration was defined as the baseline. Similarly for the primary analysis (days 11 to 19), for laboratory test results, baseline was defined as the last measurement before dose administration on day 11; for vital signs and ECGs, the baseline was the measurement obtained before dose administration on day 11.

3. Results

3.1. Safety

There was one serious AE of a preexisting condition of hypertrophic cardiomyopathy, undiagnosed before the study and detected after hospitalization for further investigation of transient ECG changes (ST segment). This finding occurred during monotherapy with citalopram. Discontinuations for AEs reported during the study included 4 subjects discontinued during the initial citalopram alone phase (3 subjects for the AEs diarrhea, urethritis and hemorrhoids, and the one subject who discontinued for the serious AE cardiomyopathy (previously described)), and 2 subjects during treatment with citalopram/lecozotan. The reasons for discontinuation of the latter 2 subjects included flu-like symptoms in 1 subject and evidence of ST in 1 subject as per the HSTC.

Overall, a total of 34 (79%) subjects reported at least one Treatment Emergent Adverse Event (TEAE) after citalopram alone (Table 1). The most commonly reported TEAEs were those previously known to be associated with citalopram administration such as asthenia, insomnia, nausea, dizziness and dry mouth. Comparatively few subjects (n=8) reported TEAEs in the citalopram/placebo group. In the citalopram/lecozotan treatment group, 20 subjects reported at least 1 TEAE. Mild dizziness and paraesthesia-like symptoms (such as tingling and electric shock sensations; head and extremities) were the most frequently reported. These TEAEs are similar to those previously reported by healthy subjects after lecozotan administration in other clinical pharmacology studies (Patat et al., 2009). There were no clinically significant AEs reported during the withdrawal phase. No significant changes in ECG, vital signs or laboratory data were observed during the study other than the ECG finding previously described.

3.2. Serotonin toxicity

The primary endpoint of this study was the proportion of subjects experiencing ST as demonstrated by the HSTC: One (1) subject, a 23-year old man, showed evidence of ST (1/21, 5%). He received 3 days of combined treatment with citalopram/lecozotan (days 11–13). Symptoms reflecting ST were observed

Table 1 Number (n>2 subjects) of subjects reporting TEAEs. ^a

Body system adverse event	CIT n=43	CIT+PBO n=17	CIT+L n=21
Any adverse event	34 (79%)	8 (47%)	20 (95%)
Asthenia	14	0	9
Headache	7	2	7
<i>Digestive system</i>			
Dry mouth	5	0	3
Nausea	8	1	5
<i>Musculoskeletal system</i>			
Muscle cramps/spasm/stiffness	4	0	2
<i>Nervous system</i>			
Depersonalization	0	1	3
Dizziness	8	1	9
Euphoria	4	0	4
Hypertonia	0	0	3
Insomnia	14	2	4
Libido decreased	4	0	0
Paraesthesia	4	0	12
Somnolence	4	0	4
Tremor	1	0	4
Trismus	3	0	1
Twitching	1	1	5
<i>Respiratory system</i>			
Rhinitis	2	0	3
<i>Skin and appendages</i>			
Sweating	4	1	3
Abnormal vision	3	0	1
Tinnitus	2	0	7

^a If the AE started during the CIT treatment period and persisted until the end of the study, it was to be counted one time in each period.

on day 13 and both treatments were withdrawn on this same day. He displayed symptoms of clinically significant hyperreflexia and profuse sweating of hands and feet. Also noted was a mild tremor of both hands. The AEs 'sweating of hands' and 'sweating of feet' resolved within 48 h (day 15) of the last drug administration. Symptoms of tremor and hyperreflexia subsided within 96 h (day 17) of the last combined dose administration. The subject was kept in the clinical unit for observation and all symptoms subsided by day 18. The symptoms observed in this subject did not evolve into 'serotonin syndrome', therefore, this event was considered to be of moderate severity by the investigator.

3.3. Pharmacokinetics/pharmacodynamics

There were no relevant differences in the mean citalopram or S-citalopram (data not shown) plasma levels following administration of citalopram alone and in combination with lecozotan 10 mg as shown in Fig. 3. The range of trough concentrations seen for lecozotan following co-administration with citalopram was similar or slightly lower than the range seen in previous clinical studies (data not shown).

Additional PK samples were taken from the subject showing signs of ST. During his time under observation in the unit, unscheduled PK samples were obtained on day 13 (hour 6), day

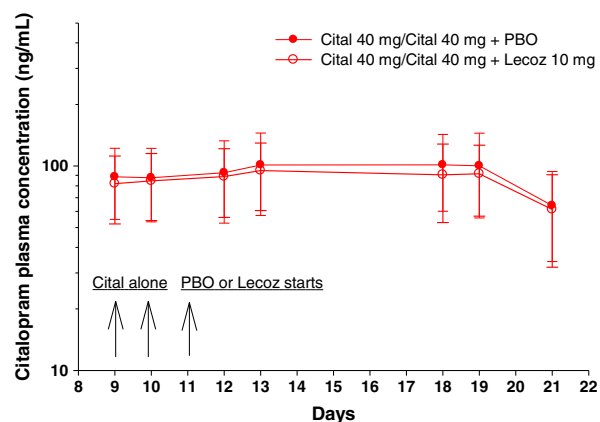


Figure 3 Citalopram plasma concentration profiles in healthy subjects receiving citalopram 40 mg alone followed by combination of citalopram 40 mg with placebo or lecozotan 10 mg (mean \pm SD).

14 (24 h following last dose) and day 15 (48 h after the last dose). This was the only subject for whom the citalopram and lecozotan plasma concentration data were obtained on day 13 (6 h), day 14 and day 15. Predose citalopram levels in this subject were below the mean value on days 9, 10, 12 and 13. Specifically, on day 13, when signs of ST appeared, the predose citalopram plasma concentration was 56.2 ng/mL (mean value of 95.0 ng/mL). The citalopram concentration at 6 h after dose administration on day 13 was 106.7 ng/mL; a slightly higher value than would be expected from historical data (Gutierrez and Abramowitz, 2000). The lecozotan plasma concentration in the subject at 6 h after dose administration on day 13 was 166 ng/mL, which was lower than the values seen at the corresponding dose and corresponding time in other studies. The lower value may have been due to lecozotan not being at steady state by day 13 after starting OD dose administration on day 11.

On study day 12, the POMS showed statistically significant increases for citalopram/lecozotan compared with citalopram/placebo for the following subscales: confusion/bewilderment ($p=0.0042$), fatigue/inertia ($p=0.0002$), tension/anxiety ($p<0.0001$), and total mood disturbance ($p=0.0001$). By day 19 there were no statistical differences between these treatments. There were no statistically significant differences between treatments in cortisol levels. However, for prolactin, statistically significant increases for combined citalopram/lecozotan in comparison to citalopram/placebo were observed on day 11 at hours 2, 4, 6, 8 and 10 as shown in Fig. 4. The highest difference between these treatments was observed on day 11 at hour 4 ($p<0.001$; $5\pm 1\ \mu\text{g/L}$, adjusted mean \pm SE). There were no clinically or statistically significant differences in temperature between treatment conditions.

4. Discussion

The HSTC has been shown to be highly sensitive to and specific for diagnosing 5-HT toxicity in a clinical setting. Here we report the novel use of this scale in a clinical

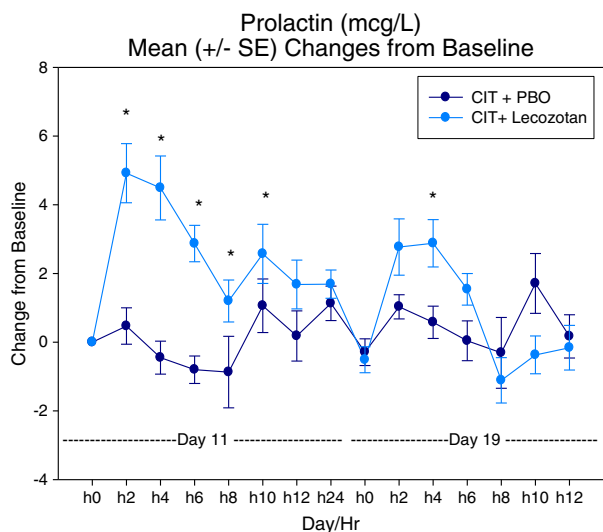


Figure 4 Prolactin ($\mu\text{g/L}$) concentration in healthy subjects receiving citalopram 40 mg with placebo or lecozotan 10 mg (mean \pm SE).

pharmacology study. The scale provided evidence of «mild serotonin toxicity» demonstrated in 1/21 subjects (5%, 95 CI [0.1%; 25.0%]) treated with citalopram/lecozotan (*versus* no event with citalopram/placebo). The finding is in accordance with data from preclinical studies reporting dose-dependent increases in 5-HT levels in the frontal cortex when lecozotan was co-administered with the SSRI fluoxetine relative to controls (unpublished data).

The trough plasma concentrations of lecozotan and citalopram in this study were in agreement with those reported in the literature (Gutierrez and Abramowitz, 2000; Patat et al., 2009). With regard to the subject who experienced ST, citalopram trough levels were below the mean value on the days surrounding the reported AE apart from day 13 hour 6 where levels were slightly higher, though importantly, due to the ST safety event, this was the only subject for whom data was collected at this time point. Based on literature reports, citalopram t_{max} is approximately 4 to 5 h and steady-state maximum concentration (C_{max}) at 40 mg OD is approximately 70 to 80 ng/mL. The citalopram plasma concentration of 106.7 ng/mL seen at 6 h after dose administration in this subject was slightly higher than the reported approximate citalopram levels following multiple dose administration of 40 mg citalopram OD (Yu et al., 2003). The onset of the ST event was around the time of peak plasma concentrations (t_{max}) of both lecozotan and citalopram. However, citalopram levels in the subject who experienced symptoms of ST were within the variability seen for citalopram. Citalopram is only a weak inhibitor of CYP2C19 both *in vitro* and *in vivo* and of CYP2D6 *in vitro*. Based on preclinical data (unpublished), lecozotan is not expected to inhibit and/or induce CYP2C19. CYP3A4 has been shown in both *in vitro* and *in vivo* clinical studies to be a major metabolic pathway for lecozotan. Lecozotan is also metabolized to a minor extent by CYP2D6 (Plotka et al., 2008). Neither of these two metabolic pathways is expected to be inhibited by citalopram at clinically relevant doses (Brosen and Naranjo, 2001). Racemic citalopram was administered in this study; the predominantly active enantiomer S-citalopram is largely metabolized by CYP2C19, and in poor metabolizers compared to extensive metabolizers (with regard to CYP2C19) – significantly higher plasma concentrations of S-citalopram have been observed, leading to the observation that a smaller dose may be required in these individuals to achieve the same level of efficacy (Herrlin et al., 2003). The CYP2C19 genotype status of the subject experiencing mild ST in the present study was not determined therefore it is unknown if a specific CYP2C19 genetic polymorphism in this individual contributed to them being more susceptible to the appearance of ST.

As described by Patat et al. (2009) in the first-in-human study of lecozotan (immediate release formulation), plasma prolactin was significantly increased around t_{max} (1–2 h) after the administration of a single 10-mg dose, and citalopram has previously been shown to elicit an augmented prolactin response when combined with the 5-HT precursor L-5-hydroxytryptophan (Lowe et al., 2006). The results described in the prolactin response observed in this study i.e. statistically significant increase during combined citalopram/lecozotan treatment support the use of prolactin as a potentially suitable biomarker to demonstrate increased 5-HT-mediated response in the synapse.

The study used an optimal design in that it was conducted in healthy subjects (carefully selected by medical and psychiatric evaluation) using a cautious approach to drug administration, with citalopram administered in ascending doses to steady state prior to the addition of lecozotan for the combined period. Moreover, the use of the HSTC provided a sensitive tool to rapidly detect any ST-related symptoms resulting from the combination of these two drugs. Given that the majority of reports of ST are based on retrospective and/or anecdotal accounts, the ability to prospectively detect its occurrence is a valuable and life-saving addition to clinical practice and/or the clinical investigation of 5-HT agents. To our knowledge this is the first reported prospective use of the scale in healthy subjects. Dingemans et al. (1998) report on a drug interaction study between the SSRI fluoxetine and the monoamine oxidase-A inhibitor moclobemide in healthy subjects; in this case, although there is a higher expectation for the occurrence of ST with this particular combination of drugs, no ST was reported. However, no specific neurological safety evaluations were reported as having been performed during this study.

The purpose of the present study was to evaluate whether combined multiple-dose administration of an SSRI, and the 5-HT_{1A} antagonist lecozotan, was safe and well tolerated and focused primarily on the risk of ST, which may occur with the combination of 2 serotonergic agents. Subjects were monitored for ST with the HSTC throughout the study. Although there were no major safety or tolerability concerns during combined treatment, evidence of ST (as defined by the HSTC) was demonstrated at neurological examination in 1 subject treated with citalopram/lecozotan. The subject's treatment was discontinued to avoid any possible progression to more severe symptoms (i.e., hyperthermia and rigidity) and the subject remained in the clinical unit for close observation. Due to the immediate discontinuation of the study drugs, whether or not this case of ST would have translated into full 'serotonin syndrome' is subject to speculation. In conclusion, the results of this study suggest that specific safety provisions should be considered when combining SSRIs and 5-HT_{1A} antagonists in clinical investigations.

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Contributors

Authors VP, SC, SR and AP designed the study and wrote the protocol. Authors JC, AP, and LS had intellectual input into the design and execution of the study. AP was the Principle Investigator who conducted the study. SR and AP undertook the analyses and VP wrote the first draft of the manuscript. All authors have contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest related to this manuscript.

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