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Specific serotonergic reuptake inhibition impairs vigilance performance acutely and after subchronic treatment

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Abstract

Subchronic treatment with the selective serotonergic reuptake inhibitors (SSRIs) fluoxetine, venlafaxine and paroxetine, but not sertraline, were previously shown to specifically impair vigilance performance. The current study was designed to compare the vigilance effects of subchronic treatment with the SSRIs sertraline and citalopram in healthy volunteers, according to a placebo-controlled, double-blind, three-way cross-over design. Twenty-four healthy subjects, aged 30–50 years, of whom 21 completed the study, underwent three treatment periods of 2 weeks in which they received sertraline (50 mg on days 1–8, 100 mg on days 8–15), citalopram (20 mg on days 1–8, 40 mg on days 8–15) and placebo. Treatment periods were separated by 14 days washout periods. Vigilance performance was assessed through a 45-min Mackworth Clock Test at days 1, 8 and 15 of each treatment period. It was found that citalopram impaired vigilance performance acutely after the first 20 mg dose and subchronically after 40 mg daily doses. By contrast, no vigilance impairment was found during sertraline treatment. Sertraline is the only SSRI studied so far with no detrimental effects on vigilance. This may be due to the affinity of sertraline for the dopamine reuptake site. Because citalopram is the most specific SSRI showing this effect, it is concluded that the SSRI-induced decrement of vigilance performance is specifically associated with serotonergic reuptake inhibition.

Keywords

citalopram, cognitive function, serotonin-drug-effects, sertraline, SSRIs, vigilance

Introduction

Vigilance decrements after acute and subchronic antidepressant administration have been reported in healthy volunteers after acute and subchronic treatment with the serotonergic reuptake inhibitors (SSRIs) fluoxetine (Ramaekers *et al*., 1995), venlafaxine (O'Hanlon *et al*., 1998) and paroxetine (Schmitt *et al*., 2002). This has led to the hypothesis that impairment of vigilance performance is associated specifically with serotonergic reuptake inhibition. The effect can be assessed after acute as well as after subchronic administration of 1–3 weeks. With the exception of sertraline, all SSRIs studied to date have been shown to impair vigilance performance using the classical Mackworth clock task (Mackworth, 1948). Briefly, the Mackworth Clock is a task that challenges continuous alertness for rare events. The Mackworth Clock Test was developed as a model to evaluate vigilance in British Air Force radar technicians during World War II (Mackworth, 1948). Subjects have to watch a clock over a continuous period of 45 min for an irregular 2-s instead of a regular 1-s jump, which on average occurs once in every 90 s. Previous studies have shown that all antidepressants including SSRIs impair performance on this task (Ramaekers *et al*., 1995; Ramaekers *et al*., 1998). However, although the impairment observed after tricyclic and second-generation antidepressants such as dothiepin and mianserin,

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respectively, can be interpreted as non-specific expressions of sedation, the vigilance impairment observed after acute and sub-chronic SSRI treatment in healthy volunteers appears to be highly specific because it is the only robust performance effect that this class of drugs appears to induce. The highly specific vigilance decrements after subchronic serotonergic drug treatment can be explained by the inhibitory effect of serotonin (5-HT) upon other neurotransmission systems maintaining arousal (i.e. the noradren-ergic, cholinergic and dopaminergic systems) (Jacobs and Fornal, 1995; Robbins, 1997). It has been suggested that subtle, but signifi-cant, affinities in SSRIs for other receptor systems (paroxetine: anticholinergic; sertraline: dopamine reuptake inhibition; venla-faxine: noradrenergic reuptake inhibition) exist and that these may explain subtle cognitive effects such as the observed long-term memory impairment after subchronic paroxetine (Schmitt *et al.*, 2001), and possibly also the absence of the vigilance decrement in sertraline. In the present study, we investigated whether citalo-pram, the most specific serotonergic drug among SSRIs, would also impair vigilance and how this compares to the vigilance effects of sertraline.

Citalopram has rarely been studied with regard to its effects on cognitive and psychomotor function. One study reported an absence of acute and subchronic cognitive and psychomotor effects of citalopram 10, 20 and 40 mg doses administered for 8 days in healthy volunteers (Fairweather *et al.*, 1997). On the basis of previous studies with other SSRIs, it would be expected that the same vigilance decrements are found in citalopram as those in fluoxetine, venlafaxine and paroxetine.

The absence of impaired vigilance performance after sertraline has been explained by the affinity of sertraline to block dopamine reuptake sites (Bolden-Watson and Richelson, 1993), and hence its property to increase dopaminergic neurotransmission. The arousal function of the dopaminergic system is characterized by that of behavioural activation (Robbins, 1997). A decline of dopamine has been proposed to underlie the classical vigilance decrement and therefore dopamine-promoting drugs are recognized as the major agents to counteract the vigilance decrement (Nicholson *et al.*, 1990). Although vigilance decrements are classically explained through an impairment of arousal caused by a lack of novel sensory input, the role of frontal executive functions (monitoring) are important as well. It is assumed that dopaminergic pathways play a major role in these functions. In our most recent study, we showed that retrieval from semantic memory, as assessed with the word fluency test, was enhanced in healthy volunteers aged 30–50 years, after subchronic sertraline administration relative to placebo. This improvement was not seen after paroxetine (Schmitt *et al.*, 2001). The explanation foor this effect could lie in a relatively enhanced dopaminergic function because this is important in executive, frontal lobe functions such as memory retrieval. The present study aimed to demonstrate that subtle differences in pharmacological profiles among the SSRIs sertraline and citalo-pram have demonstrable and differential behavioural effects on vigilance performance, as well as performance on tests of memory and psychomotor function.

We hypothesized impairment of vigilance performance as determined by performance on the Mackworth Clock test in healthy middle-aged volunteers after treatment with therapeutic doses of citalopram in comparison with placebo on days 1, 8 and 15 of treatment, respectively.

Secondarily, we investigated the same hypothesis for an effect of sertraline on Mackworth clock performance. Furthermore, we investigated if citalopram and sertraline had any effect on perform-ance in other cognitive and psychomotor tasks.

Materials and methods

Subjects

Twenty-four healthy volunteers of both sexes, aged 30–50 years, participated in the study (Table 1). Screening included a telephone interview, health questionnaire, 12-lead electrocardiogram, labora-tory tests (blood haematology and chemistry, urinalysis, drug and pregnancy screening) and a routine medical examination. Exclu-sion criteria were the presence or a history, cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, haematological or psychiatric illness, symptoms excessive drinking (> 20 units of alcohol per week) pregnancy or lactation, use of medication other than oral contraceptives, use of drugs, and any sensory or motor deficits which could reasonably be expected to affect test perform-ance. All subjects scored below depression threshold (< 50) on the Zung Depression Scale (Zung, 1965). The study was approved by the standing Medical Ethics Committee of Maastricht University, and carried out in accordance with the Declaration of Helsinki (Hong Kong Modification, 1989). Written informed consent was obtained from each subject prior to participation.

Experimental design

Double-blind, placebo-controlled, three-way cross-over study. Complete balancing of the treatment orders yielded six treatment orders distributed over 24 subjects.

Treatment

Treatment orders were randomly assigned and double-blind. Treatment periods lasted 15 days and were separated by 13-day washout periods. Treatment regimens consisted of sertraline 50 mg o.d. on days 1–8, followed by sertraline 100 mg o.d. on days 9–15; citalopram 20 mg o.d. on days 1–8, followed by citalopram 40 mg o.d. on days 9–15, or placebo. Medication was taken at fixed times

Table 1 Subject variables

	Mean ± SE	Min – Max
Males/females	11/10	
Age (years)	40.3 ± 1.1	30–49
Level of edcucation (1–7)	2.6 ± 0.4	1–6
Body mass index (weight/length^2)	24.9 ± 0.7	20–32
Zung Depression Score	28.7 ± 1.5	21–46

Data are mean ± SE.

in the morning in one capsule during the first week and two capsules during the second week. At the investigated daily dosages, which typical resemble start dose regimens in clinically depressed patients, both SSRIs are equally efficacious in the treatment of major depression (Goodnick and Goldstein, 1998).

Procedure

All medication was taken orally either always at 08.00 h (subjects 2, 15, 18, 20, 21, 22, 23, 24), at 10.00 h (subjects 1, 5, 6, 9, 10, 12, 13, 14) or at 12.00 h (subjects 3, 4, 7, 8, 11, 16, 17, 19). Assessments were always carrried out starting 4 h after drug administration and lasting until 6 h after drug administration. Blood samples for drug levels were taken 6 h after drug administration.

Assessments were done on days 1, 8 and 15 of each treatment period on a fixed time between 12.00 h and 18.00 h. Before the start of the study, all subjects were individually trained to practice cognitive tests. Consumption of alcoholic beverages during the treatment periods was prohibited and subjects were instructed to arrive at the laboratory well rested. Female subjects were tested for pregnancy before the start of each the three treatment periods. The entire procedure lasted approximately 2 h.

Upon arrival, subjects completed the Groningen Sleep Quality Scale (see below) and were then seated in a soundproof test room. They first completed the word learning and reaction time tests (see below). Subsequently, vigilance performance was assessed using a 45-min Mackworth Clock Test (see below). Finally, a 10 ml blood sample was taken.

Cognitive test battery

Mackworth Clock Test (Mackworth, 1948) This test has been extensively used in studies on human vigilance performance. Subjects were seated in front of a computer screen displaying a circular arrangement of 60 dots simulating the second marks on a clock. Dots were briefly illuminated in clockwise rotation at a rate of one per 500 ms. Usually the rotation proceeded with a 6° jump. Subjects were instructed that at rare, irregular intervals the target would proceed with a 12° jump by skipping one of the dots in the normal sequence. This double jump was the signal to which subjects were required to respond by pressing a button as quickly as possible. A response made within 4 s after the occurrence of a signal was registered as a correct detection. A total of 30 signals were presented during the 45-min task. Ten signals occurred within each successive 15-min period, with intervals ranging from 8 s to 7.2 min. Outcome measures were the number of correct detections and the corresponding reaction times, and the number of false detections.

Word Learning Test (Riedel et al., 1999a) This test is an adapted version of the Rey Auditory Verbal Learning Test (Lezak, 1995). The test consists of a list of 30 monosyllabic words (18 nouns and 12 adjectives), which are presented in three trials on a computer screen. Items are presented in the same sequence at a rate of one per 2 s. Each trial ends with a free recall of the words (immediate recall). Thirty minutes after the third trial, the subject

is requested to recall as many words as possible (delayed recall). A Yes/No recognition test, consisting of 15 former words and 15 new but comparable words, is given after the delayed recall test. The words remain on the screen for 2000 ms or until the subject responds. Another 1000 ms elapse before the next word appears on the screen. After presentation of each word the subject has to respond 'Yes/No' as fast as possible to indicate recognition of the word (delayed recognition). The reaction times (RTs) are recorded. There are two different recognition lists to probe the long term retention of each 30 word list. Both recognition lists consist of 15 formerly learned and 15 new words (distractors). According to the theory of signal detection (Pollack and Norman, 1964), the proportion of correctly recognized words (*cr*) and the proportion of falsely recognized (*fr*) constitute the nonparametric sensitivity measure: $A' = 1 - \frac{1}{4}[fr/cr + (1 - cr)/(1 - fr)]$. A' is in fact the proportion of correctly recognized words, corrected for the subject's response tendency. Because the distribution of A' is skewed due to a ceiling effect, A' should be arcsin transformed before being used in statistical analysis. The variables used are the total number of words recalled after the first three trials as a measure of short-term memory, the number of correct words on delayed free recall as a measure of retrieval from long-term memory (LTM), A' as a measure of storage in LTM, and the median RT of correctly recognized target words as a measure of speed of retrieval from LTM. There are six parallel lists, comparable with regard to their level of abstraction and the affective tone of the words. The six lists of 30 words, each contain 18 nouns and 12 adjectives. All words are monosyllabic and meaningful. The words were chosen from a list of 600 words. The lists are comparable with respect to their amount of abstraction. For each recognition version, 15 target words were taken, to which 15 distractor words were added. Both the target words and the distractors are similar in their level of abstraction.

Simple- and choice-reaction time (Houx and Jolles, 1993) This is a computerized test, in which reaction times are studied as a function of the complexity of task requirements. In addition, the speed and accuracy of arm movements over short trajectories are also studied. The subject held one button and was asked to press one of five other buttons located equidistantly from the hold button when lit. This yielded reaction times consisting of an initiation phase (time from stimulus onset until release of the hold button) and a movement phase (time from release of the hold button until the response button is pushed). The response set consisted of pressing the one button that lit up (simple RT), pressing one of three buttons which lit up (three-choice RT), or pressing the button to the right of the lit button (Stimulus–Response incompatible three-choice RT) as quickly as possible. Initiation times and movement times thus comprised the dependent variables obtained for each of the three reaction time tasks. This task measures sensorimotor speed, choice-reaction speed, and choice-reaction speed with response competition.

Profile of Mood States (POMS) (McNair et al., 1992) The POMS is a self-evaluation scale for short, alternating states. The POMS consists of 72 adjectives comprising six bipolar mood factors (Energetic–Tired, Elated–Depressed, Agreeable–Hostile,

Confident–Unsure, Composed–Anxious and Clearheaded–Confused). Next to each adjective is a five-point scale. In this way, the respondent can indicate in what amount these items are appropriate to his/her mood.

Subjective Sleep Quality Subjective quality of sleep was assessed using the Groningen Sleep Quality Questionnaire (Mulder-Hajonides-van-der-Meulen, 1981). This questionnaire consists of 14 items denoting statements regarding the quality of sleep over the past week. The items are transitive and refer to sleep problems of increasing severity and hence form a Gutman-Scale, but its items are presented in random order. Subjects agreed or disagreed with each of the statements. Maximum score is 14, indicating severely disturbed sleep, and minimum score is 0, indicating no sleep problems.

Blood sampling

Blood (10 ml) was collected by venipuncture on days 1, 8 and 15 at the end of each cognitive test battery. Blood samples obtained in the citalopram and sertraline periods were assayed for the appropriate drug using a reverse phase high-performance liquid chromatography procedure with ultraviolet detection, with a detection limit of 10 ng/ml for the citalopram assay and 5 ng/ml for the sertraline assay.

Statistical analysis

The primary outcome measure, correct detections on the Mackworth Clock Task, was evaluated using repeated measures ANOVA of the vigilance assessments at days 1, 8 and 15 for the comparison between citalopram and placebo. Due to the one-sided nature of the prediction of impairment after citalopram, only in this primary endpoint evaluation, one-tailed significance testing was carried out. All other evaluations were carried out in a similar fashion, but were tested two-tailed and $\alpha = 0.05$ in all cases.

The number of subjects is sufficient to detect a performance impairment of one target out of 30 in the Mackworth Clock Vigilance Task (Ramaekers *et al.*, 1995; O'Hanlon *et al.*, 1998; Schmitt *et al.*, 2002). This impairment can be considered safety relevant because it resembles an extra amount of time of inattention or 'off the job' of 2 min per hour as a result of drug side-effects, which is enough time for the incipience of accidents.

Results

Twenty-one subjects completed the study. Three subjects (one male and two females) did not complete the study due to side-effects. One male subject stopped participation after the first dose of citalopram 20 mg, which happened to be the first dose in the

Table 2 Cognitive measures on days 1, 8 and 15 of placebo, sertraline and citalopram treatment

Task	Outcome parameter	Treatment	Day 1 (acute effect of low dose)	Day 8 (subchronic effect low dose)	Day 15 (subchronic effect high dose)
Word list learning	Maximum no. words immediate recall	Placebo	15.9 ± 1.0	12.9 ± 0.8	12.7 ± 0.8
		Sertraline	16.7 ± 1.3	13.1 ± 0.8	14.0 ± 1.0
		Citalopram	16.9 ± 1.2	13.0 ± 1.0	12.9 ± 0.9
	No. words delayed recall	Placebo	12.4 ± 1.4	11.1 ± 1.2	12.0 ± 1.2
		Sertraline	13.6 ± 1.5	11.3 ± 1.0	11.5 ± 1.5
		Citalopram	12.8 ± 1.4	10.9 ± 1.4	10.5 ± 1.3
	% Correct words delayed recognition	Placebo	27.0 ± 0.5	25.6 ± 0.6	25.4 ± 0.6
		Sertraline	25.4 ± 1.1	25.9 ± 0.5	25.6 ± 0.6
		Citalopram	26.1 ± 0.7	25.4 ± 0.7	25.9 ± 0.5
	RT delayed recognition (ms)	Placebo	810 ± 20	814 ± 19	792 ± 20
		Sertraline	798 ± 17	836 ± 28	794 ± 19
		Citalopram	803 ± 21	821 ± 18	823 ± 22
Motor and choice reaction time	Movement time (ms)	Placebo	118 ± 5	115 ± 4	113 ± 5
		Sertraline	114 ± 5	114 ± 5	113 ± 5
		Citalopram	110 ± 4	113 ± 4	112 ± 5
	Simple RT (ms)	Placebo	309 ± 8	300 ± 7	297 ± 6
		Sertraline	304 ± 9	292 ± 8	294 ± 7
		Citalopram	296 ± 9	290 ± 8	291 ± 8
	Chioce RT (ms)	Placebo	364 ± 11	361 ± 8	357 ± 9
		Sertraline	356 ± 8	359 ± 9	352 ± 8
		Citalopram	351 ± 8	347 ± 9	350 ± 7
	Improbable choice RT (ms)	Placebo	447 ± 14	444 ± 14	433 ± 14
		Sertraline	437 ± 17	429 ± 15	436 ± 16
		Citalopram	435 ± 13	428 ± 14	430 ± 13

Data are mean ± SE. RT, Reaction time.

Table 3 Subjective measures on days 1, 8 and 15 of placebo, sertraline and citalopram treatment

Task	Outcome parameter	Treatment	Day 1 (acute effect of low dose)	Day 8 (subchronic effect low dose)	Day 15 (subchronic effect high dose)
Subjective sleep measures	No. complaints	Placebo	2.6 ± 0.7	3.2 ± 0.9	1.7 ± 0.6
		Sertraline	2.0 ± 0.7	2.5 ± 0.5	3.8 ± 0.9
		Citalopram	2.1 ± 0.7	2.9 ± 1.0	3.3 ± 0.7
	Sleep latency (min)	Placebo	15 ± 3	22 ± 9	14 ± 3
		Sertraline	11 ± 2	15 ± 3	25 ± 9
		Citalopram	16 ± 4	15 ± 4	17 ± 3
	Sleep duration (h)	Placebo	7.1 ± 0.2	6.7 ± 0.4	7.4 ± 0.2
		Sertraline	7.3 ± 0.3	7.2 ± 0.3	6.9 ± 0.3
		Citalopram	7.3 ± 0.2	7.1 ± 0.3	7.1 ± 0.3
	No. awakenings	Placebo	1.0 ± 0.3	1.0 ± 0.3	0.7 ± 0.3
		Sertraline	0.7 ± 0.2	1.0 ± 0.3	1.1 ± 0.4
		Citalopram	0.6 ± 0.3	1.0 ± 0.3	1.6 ± 0.4
Profile of mood states	Depression (0–100)	Placebo	14 ± 3	16 ± 4	18 ± 3
		Sertraline	19 ± 4	19 ± 3	19 ± 3
		Citalopram	17 ± 3	17 ± 3	17 ± 4
	Anger (0–100)	Placebo	14 ± 2	16 ± 3	19 ± 4
		Sertraline	19 ± 4	20 ± 3	20 ± 4
		Citalopram	18 ± 3	18 ± 3	18 ± 4
	Fatigue (0–100)	Placebo	21 ± 4	23 ± 4	23 ± 4
		Sertraline	30 ± 5	27 ± 4	27 ± 4
		Citalopram	25 ± 4	26 ± 4	29 ± 4
	Vigour (0–100)	Placebo	83 ± 4	79 ± 4	78 ± 4
		Sertraline	74 ± 4	75 ± 4	75 ± 4
		Citalopram	77 ± 4	77 ± 4	73 ± 4
	Tension (0–100)	Placebo	16 ± 3	17 ± 3	20 ± 4
		Sertraline	21 ± 4	21 ± 4	20 ± 3
		Citalopram	18 ± 3	18 ± 3	19 ± 3

Data are mean ± SE.

first session. This subject complained about nausea and diarrhoea. One female subject also halted participation after the first dose of citalopram 20 mg, which happened in the third treatment period (meaning that she did finish the other two conditions). She complained about nausea and lightheadedness. Another female subject stopped after the eight daily dose of citalopram 20 mg and completed the other treatments. She complained about nausea and loss of appetite. All these subjects' complaints were said to be of a serious nature, such that they led to their decision to halt the respective treatment conditions, which all turned out to be citalopram 20 mg.

Performance and mood results are shown in Tables 2 and 3, respectively.

Mackworth Clock

Analysis of the number of correct responses over the 45-min vigilance task showed that citalopram reduced the number of correct responses [$F(1,20) = 3.4$, $p = 0.041$] (Fig. 1). Sertraline did not significantly affect correct responses in the vigilance task. No main effect of Treatment by Day emerged from either drug–placebo comparison. Reaction times for the correct responses showed that sertraline accelerated responses [$F(1,20) = 5.7$, $p = 0.027$].

Simple- and Choice RT

There was no main effect of citalopram on RT in either of the three subtasks, but there was a treatment by day interaction which seemed to indicate that citalopram speeded overall RT on the first day of treatment and that the effect subsided as treatment duration continued [$F(1,20) = 5.1$, $p = 0.035$]. A similar effect of citalopram on 3-choice RT [$F(1,20) = 5.6$, $p = 0.029$] was seen in the absence of treatment by day interactions.

Word list

No effects on immediate recall were seen. Citalopram impaired delayed recall on day 15 as indicated by a significant treatment by day interaction [$F(1,20) = 5.5$, $p = 0.030$]. No other effects on delayed recall were seen. No significant effects were seen on recognition parameters.

Subjective Sleep Questionnaire

No treatment effects or interactions were seen on subjective sleep quality, sleep latency and sleep duration.
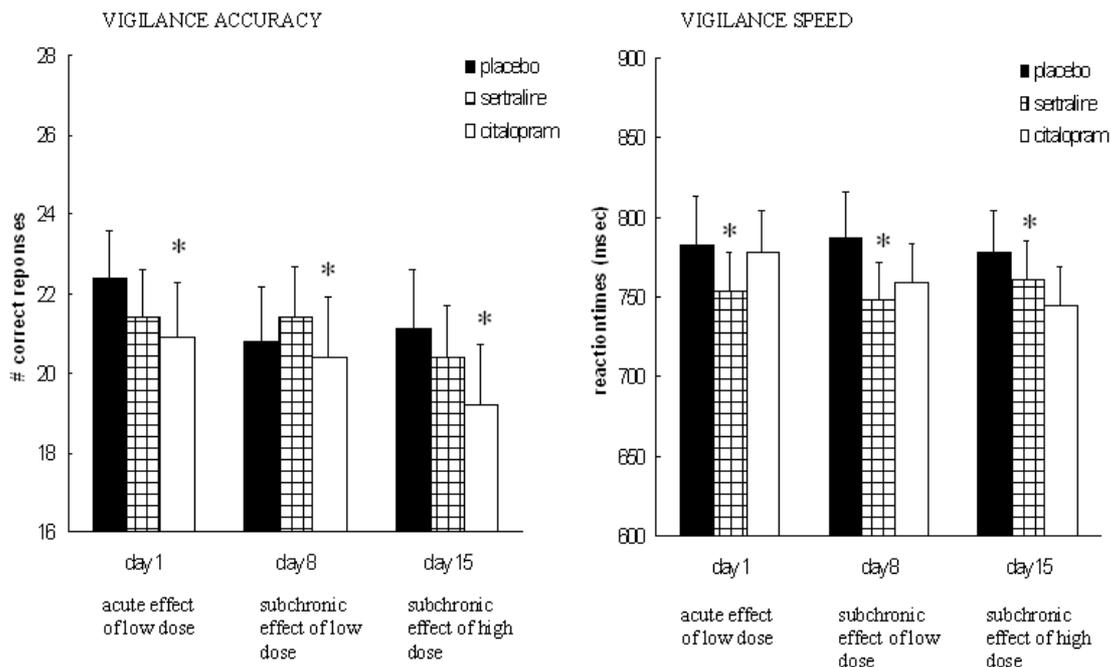
Figure 1 Mean ± SE number of correct responses (left) and the corresponding response times (right) in the Mackworth vigilance task following 1, 8 and 15 days of treatments with placebo, sertraline and citalopram. *$p < 0.05$ versus placebo

Profile of Mood States

Sertraline [$F(1,20) = 5.1$, $p = 0.036$] and citalopram [$F(1,20) = 7.0$, $p = 0.016$] decreased feelings of vigour. Citalopram [$F(1,20) = 5.0$, $p = 0.038$] increased feelings of fatigue. No effects were observed on the POMS dimensions depression, anger and tension.

Drug plasma levels

Plasma levels [main effect: $F(2,19) = 124$, $p < 0.0001$] of sertraline [$F(1,20) = 98$, $p < 0.001$] and citalopram [$F(1,20) = 244$, $p < 0.001$]
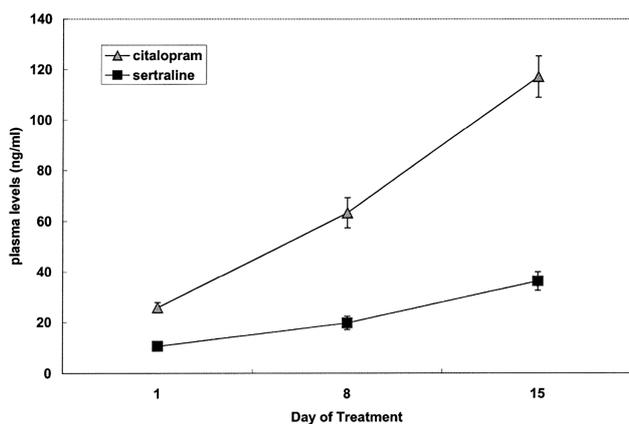

Figure 2 Drug plasma levels

significantly differed from zero from the first day of treatment (Fig. 2) and linearly increased throughout the treatment period (interaction effect: $F(2,19) = 39$, $p < 0.001$], both for sertraline [$F(1,20) = 61$, $p < 0.001$] and citalopram [$F(1,20) = 164$, $p < 0.001$].

Effects of gender

No significant differences emerged between males and females in any of the dependent variables. However, it must be noted that sample sizes were not large enough to conclude absence of gender differences in the observed effects.

Effects of time of day

No significant differences emerged between subjects tested at different times of day in any of the dependent variables. It seems unlikely that the three cohorts of subjects in whom drug administration and cognitive testing was spaced 2 h apart has influenced the results.

Effects of treatment order

Treatment orders were completely counterbalanced for 24 subjects. Two subjects dropped out on citalopram in the first treatment period and one in the third treatment period, rendering a slight imbalance in treatment orders. However, upon inspection of the data, it seems unlikely that this was of any influence on the results.

Discussion

Briefly summarizing the results, we note that the prediction that citalopram would impair the primary outcome measure, vigilance performance, was confirmed, albeit that the effect was marginal. As in the previous study (Schmitt *et al.*, 2002), sertraline did not impair vigilance performance. Furthermore, three subjects dropped out from the citalopram condition due to gastric adverse effects of citalopram. Results could not be corrected for this selective dropout. Sertraline speeded reaction times in the Mackworth vigilance task. This was also observed in the previous study (Schmitt *et al.*, 2002). Citalopram tended to impair delayed recall after 2 weeks of treatment and tended to accelerate RT in the choice RT task but, otherwise, no effects on cognition were found. Both SSRIs had no effects on subjective sleep quality, but subjective measures of mood showed that both tended to decrease feelings of vigour and citalopram tended to increase feelings of fatigue. Plasma levels of both drugs were significantly elevated after single doses and remained increased after 1 and 2 weeks of treatment.

Vigilance

The pharmacological differences between antidepressants studied using the Mackworth Clock vigilance paradigm appear to indicate that enhancing 5-HT in normal individuals consistently impairs vigilance, just as anticholinergic and antihistaminergic drugs tend to. The simultaneous enhancement of noradrenaline with 5-HT in venlafaxine was previously shown not to counteract the vigilance decrement (O'Hanlon *et al.*, 1998). This means that the decrement is not associated with decreased activity of a serotonergic-noradrenergic system or, alternatively, that the noradrenaline reuptake blocking properties of venlafaxine are not strong enough. Although this is the only human study perfomed *in vivo* that points in this direction, there is abundant evidence from animal studies that noradrenaline is not the critical neurotransmitter specifically associated with the maintenance of vigilance (Delagrange *et al.*, 1993; McGaughy *et al.*, 1997). It is more likely that noradrenaline is associated with phasic arousal, whereas dopamine is more likely to be associated with a tonic readiness to respond (Pribram and McGuinness, 1975; Robbins, 1997). The lack of effect of sertraline on correct detections in the vigilance task and the tendency of sertraline to speed responses in the vigilance task appears to be consistent with the notion that sertraline differs from the other SSRIs mainly in terms of its additional dopaminergic reuptake inhibition properties (Schmitt *et al.*, 2002).

The vigilance effect of SSRIs is not large, but can be considered theoretically and practically relevant. Possible negative effects on vigilant behaviour should be considered when prescribing SSRI treatment, especially to individuals in occupations requiring alert behaviour in monotonous situations over longer periods of time.

Reaction time tasks

We observed speeding of three-choice RT after citalopram. Such an observation is in line with a previous report showing that the SSRI fluvoxamine accelerated RT and improved information processing *per se* (Hasbroucq *et al.*, 1997). The authors suggested that fluvoxamine did not act on the processing stages of stimulus preprocessing and response selection, but improved speed of information processing. However, we did not see any significant SSRI-induced changes of movement time, Simple RT and incompatible three-choice RT. Because of the small effect size as well as potential confounding due to multiple testing, the data described here require replication before further interpretations are made and conclusions drawn.

Memory

In a previous study that was very similar to the current one, we found impaired delayed recall performance after paroxetine, but not sertraline (Schmitt *et al.*, 2001). These results were explained by the non-serotonergic properties of both drugs (i.e. the anticholinergic affinity of paroxetine was taken to account for impaired delayed recall). However, in the present study, we found a tendency of citalopram to impair delayed recall memory after 15 days of treatment. Therefore, we now have to consider the possibility that elevated levels of 5-HT, rather than anticholinergic effects explain delayed recall memory impairment at day 15 of administration of citalopram. This is not directly in line with the recent observation that an acute dose of citalopram 10 mg i.v. facilitated memory consolidation (Harmer, 2002). However, the different dose and route of administration complicate any comparison. Improvement of memory after serotonergic antidepressants has also been reported in clinical studies (Fudge *et al.*, 1990; Riedel *et al.*, 1999b; Levkovitz *et al.*, 2002), but the mechanism remains unknown.

Subjective effects: sleep and mood

Both citalopram and sertraline reduced vigour and citalopram elevated fatigue, an observation which is in line with others describing a positive association between elevated levels of 5-HT and fatigue in healthy individuals (Struder and Weicker, 2001). These effects of elevated 5-HT on vigour and fatigue might be consistent with the impairment of vigilance performance, especially in the case of fatigue, leaving undecided only whether these POMS items are simply more sensitive then prolonged vigilance performance, or are indicative of a different process, because only citalopram impaired vigilance performance and not sertraline. To investigate whether there was an association between SSRI effects on vigilance and on vigour and fatigue within subjects, analyses of correlations of drug placebo difference scores between vigilance correct detections and POMS items vigour and fatigue were carried out. The pearson correlation coefficients of vigilance with vigour and fatigue were both $r = 0.38$ for sertraline on the first day, but these correlations were not significant. All other coefficients were between $r = -0.12$ and $r = 0.16$ and were non-significant.

There are no reports that antidepressants improve depressive symptoms in non-depressed patients. However, the cut-off for depression used in the current study (Zung < 50), although

formally the cut-off used by Zung (1965), will actually permit a fair amount of depressive symptoms to be experienced by the subjects. Note that the maximum score for the Zung is 80 and that in the case of the Beck Depression Inventory, the cut-off for 'not-depressed' of 12 is less than 20% of the total range of the scale (64). Although we did not collect Zung ratings during the study, it would have been interesting to see if there were any changes in the scores. However, the only alternative measure to answer this question is the POMS depression subscale and, clearly, no changes were detected in this subscale. The POMS depression subscale has been shown to be sensitive to serotonergic manipulations in similar studies in healthy volunteers on tryptophan depletion (Klaassen *et al.*, 1999) and specifically sensitive to discriminate both between depressed and healthy individuals, as well as the effects of a serotonergic agonist, *m*-chlorophenylpiperzine (Riedel *et al.*, 2002). Therefore, it is unlikely that the observed SSRI effects on cognition, fatigue and vigour are mediated through their primary effects on mood.

Plasma drug levels

Plasma drug levels of citalopram and sertraline that rise throughout the study reflect a high degree of compliance of the subjects in general.

There was a significant inverse association of citalopram plasma with vigilance performance on on the first day. At 3 h after drug administration, there was a negative correlation of the difference scores of both accuracy of vigilance performance ($r = -0.47$, $p < 0.05$) and speed of response ($r = -0.46$, $p < 0.05$). The direction of this association indicates that high plasma citalopram concentrations were associated with improved performance and low concentrations with impaired performance. In view of the fact that, on average, the acute effect of citalopram was to impair performance, more detailed inspection of the data shows that of 21 subjects, 12 performed worse after acute citalopram and seven performed better, whereas two showed no change.

After 15 days of citalopram treatment, the association of plasma levels with reaction times had reversed in the opposite direction, indicating that higher levels were now associated with impaiment ($r = +0.44$, $p < 0.05$).

Clinical relevance

More work needs to be carried out to confirm whether the present findings can be reproduced in patients. However, occasional reports of sedation in patients on SSRI treatment appear to be supported by the abundant experimental data on SSRIs demonstrating effects on vigilance.

Conclusion

The main findings of this study are that citalopram impaired vigilance performance. By contrast, no vigilance impairment was found during sertraline treatment. No other cognitive or behavioural effects were found that could account for the effect of citalopram on vigilance.

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