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The effects of acute treatment with paroxetine, amitriptyline, and placebo on driving performance and cognitive function in healthy Japanese subjects: A double-blind crossover trial

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Objective To assess the effects of antidepressants on driving performance from a different methodological viewpoint in light of the recent traffic accidents.
Methods In this double-blinded, 3-way crossover trial, 17 healthy males received acute doses of 10 mg paroxetine, 25 mg amitriptyline, and placebo. The subjects were administered three driving tasks—road tracking, car following, and harsh braking—performed using a driving simulator and three cognitive tasks—Wisconsin Card Sorting Test, Continuous Performance Test, and N-back test at baseline and at 1 h and 4 h post-dosing. The Stanford Sleepiness Scale scores were also assessed.
Results At 4 h post-dosing, amitriptyline significantly impaired road-tracking and car-following performance, reduced driver vigilance, and caused subjective somnolence. Paroxetine impaired neither driving performance nor cognitive function.
Conclusions Acute doses of amitriptyline significantly impaired driving performance in the context of driving on crowded urban roads at relatively low speeds. This setting is important with respect to skills necessary for daily driving and may be difficult to measure in actual driving tests. This simulator-based study replicated the results of previous studies and could be considered complementary to them. This method may enable easy and safe screening of the driving hazard potential of drugs.

KEY WORDS — antidepressants; paroxetine; amitriptyline; driving performance; cognitive function

INTRODUCTION

Most of the currently available antidepressants have similar therapeutic efficacies, regardless of whether they are selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) (Anderson, 2000). The choice of an antidepressant is therefore largely determined by its side effects and the tolerability profile of an individual. According to their pharmacological profiles, antidepressants can impair cognition. Although continuous antidepressant therapy is required for patients with recurrent depressive disorders to prevent relapse (Geddes *et al.*, 2003) and improve their social and occupational lives, the unpleasant side effects could force them to discontinue treatment (Nemeroff, 2003) and may impair their daily activities, including driving in a motorized society.

Epidemiological data indicate that compared to nonusers, TCA users are twice as likely to be involved in traffic accidents (Leveille *et al.*, 1994; Ray *et al.*, 1992). Given the cross-sectional nature of these studies, no study has clarified the causal relationship

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between antidepressants and traffic accidents. Various effects of antidepressants on driving performance were recently evaluated in healthy subjects (Kerr *et al.*, 1996; Ridout and Hindmarch, 2001; Ridout *et al.*, 2003; Robbe and O'Hanlon, 1995; Wingen *et al.*, 2005) and depressed patients (Brunnauer *et al.*, 2006; Wingen *et al.*, 2006). Most of these recent studies used actual driving tests to measure driving performance. In these tests, the driving tasks were designed to reproduce real-life situations; however, these tasks addressed only certain aspects of driving because of the inherent safety risks and measurement limits of actual driving tests. Meanwhile, rear-end collisions account for nearly 30% of all traffic accidents in both Japan (National Police Agency Transportation Authority, 2007) and the United States (National Highway Traffic Safety Administration, U. S. Department of Transportation, 2007). It is imperative that a driver's ability to maintain a contextually appropriate following distance be reviewed to avoid rear-end collisions (Brookhuis *et al.*, 1994). Previous car-following tests (Brookhuis *et al.*, 1994; Ramaekers *et al.*, 1995; Ramaekers *et al.*, 2002) focused on the perception of speed deceleration of a leading car traveling at relatively high speeds and on safe following distance. The car-following performance in the context of driving at relatively low speeds on crowded urban roads has not been fully examined thus far and may be difficult to evaluate in actual driving tests.

Car driving is a complex task requiring many cognitive processes, including perception, attention, learning, memory, decision making, and action control. Therefore, the effects of antidepressants should be evaluated in terms of not only the driving performance but also each cognitive function. Previous studies used conventional tasks such as the critical flicker-fusion frequency task, divided attention task, and choice reaction time task for assessing the cognitive function. Such studies are prone to yielding varying results, depending on the type of cognitive task utilized. Therefore, it is important to employ widely used tasks that are more complicated than conventional tasks. The Wisconsin Card Sorting Test (WCST), Continuous Performance Test (CPT), and N-back test are examples of the desired complicated tasks, and the neural correlates of these tasks involve broad cortical areas, particularly the frontal cortex, which is related to driving skills. However, the effects of antidepressants on these three tasks have not yet been fully elucidated.

Thus, the aim of the present study was to evaluate the influences of acute paroxetine or amitriptyline treatment on driving performance, particularly in the context of the recent traffic accidents. We used simulator scenarios to examine the car-following performance in the context of driving on crowded urban roads at relatively low speeds. In addition, other established driving performance variables were also measured in the simulator scenario. Furthermore, the cognitive functions of subjects were evaluated by the WCST, CPT, and N-back test.

METHODS

Subjects

The study recruited 17 healthy male volunteers aged 30–42 years (mean ± SD, 35.8 ± 3.3 years). Only male subjects were included in the study because the changes in hormone levels occurring during the menstrual cycle can substantially affect cognition in healthy women (Hampson, 1990; Maki *et al.*, 2002; Phillips and Sherwin, 1992). All subjects had held a driving license for at least 10 years and drove a car daily for a minimum of 5000 km per year. All participants were drug-free prior to the study. Health interviews and the Structured Clinical Interview for DSM-IV (SCID) conducted at the time of the study indicated that none of the participants had any physical or psychiatric disorders. The study was approved by the ethics committee of the Nagoya University School of Medicine, and written informed consent was obtained from each subject prior to participation.

Study design

The study used a randomized, double-blind, placebo-controlled, 3-way crossover design. The subjects received acute doses of 10 mg paroxetine, 25 mg amitriptyline, and matched placebo in three different treatment sessions. The doses selected were based on generally recommended clinical starting dose, and minimizing possible risks of side effects, such as nausea and vomiting, which could confound the results. There was a washout period of at least 7 days between the treatment sessions, and the medications and placebo were presented as identical capsules.

Testing procedure

The subjects received substantial training in driving and cognitive tests 1 or 2 weeks prior to first testing; in order to minimize the learning effects, the subjects were trained until they reached the plateau level. On

each test day, the participants arrived at the laboratory at 9:00 AM and filled out self-rating questionnaires. Under baseline conditions, the driving tests started at 9:30 AM and lasted for approximately 15 min, while the cognitive tests started at 10:00 AM and took approximately 30 min. After the baseline assessment, each subject was administered one of the three drugs. The assessments of driving skills and cognitive function were repeated at 1 h and 4 h post-dosing.

Furthermore, the subjects were prohibited from consuming alcohol or caffeinated beverages for 12 h before testing and were directed to sleep adequately on the eve of testing. On the test days, the subjects were also prohibited from ingesting caffeine, supplement drinks, chewing gum, or candies to stay awake since these substances could exert a stimulating effect on their performance. During the intervals between the test batteries, the subjects were given light tasks to prevent short naps.

Driving performance

We divided the daily driving skills associated with traffic accidents into three tasks. A driving simulator (Toyota Central R&D Labs, Inc., Nagakute, Japan) was used to test the driving performance; the same simulator was used in a previous functional magnetic resonance imaging study to determine the neural substrates of driving skills (Uchiyama *et al.*, 2003). This simulator software was run on a personal computer (PC) (Windows XP) equipped with a steering wheel, accelerator, and brake pedal system (SIDEWINDER; Microsoft). Images from the PC were projected onto a 1620×1220 mm^2 screen via an LCD projector (TH-LB30NT; Panasonic, Osaka, Japan). While watching the driving scenes on the screen, the subjects controlled the speed and position of their car by manipulating the steering wheel, accelerator, and brake pedal. The driving simulation was conducted in a dark, sound-attenuated room.

Road-tracking test

The gently winding 2-lane road with no other traffic continued throughout the test duration of 5 min. The subjects were instructed to drive at a constant speed of 100 km/h and stabilize the vehicle in the center of the left lane. The lateral position of the vehicle (in cm) from the right edge of the left lane was recorded every 10 ms. The standard deviation of the lateral position (SDLP; in cm), which indicates weaving, was taken as a performance measure. This test is based on a road-tracking test developed previously (O'Hanlon, 1984; O'Hanlon *et al.*, 1982).

Car-following test

The test included a straight 2-lane road with no other traffic, except for a single preceding car. When the preceding car decelerated, its brake lights came on. As the preceding car accelerated (to 60 km/h) or decelerated (to 40 km/h), the subject was required to maintain the distance between the cars as close to 5 m as possible. The car-following distance (m) was recorded every 10 ms, and performance was measured as the coefficient of variation (CV) obtained by dividing the standard deviation of the distance between the cars by the mean value (Uchiyama *et al.*, 2003). Therefore, a smaller distance CV value (DCV) indicated better performance. The test duration was 5 min.

Harsh-braking test

The test included a straight 2-lane road with no traffic, but with humanoid models on either side of the left lane. The humanoid models randomly ran onto the road as the subject's car approached. The subject was instructed to maintain a constant speed of 50 km/h and to avoid hitting the humanoid models by harsh braking as quickly as possible. As described previously (Hindmarch *et al.*, 1983; Ridout and Hindmarch, 2001), the brake reaction time (BRT; in ms) was used as a measure of the cognitive psychomotor performance, including attention efficiency. Each test consisted of 7 BRT trials over a 5-min period, and the mean BRT was calculated from these results.

Cognitive function

The cognitive test battery consisted of 3 tasks performed on a PC by manipulating a computer mouse or numeric keypad.

WCST

The WCST (Heaton, 1981) was used to measure the executive function, for example, abstract reasoning ability or the ability to shift cognitive strategies in response to changing environmental contingencies. A modified computerized version of the WCST (Kashima *et al.*, 1987) was administered, and the test lasted until such time as 48 cards were sorted. In this study, performance was measured by the following indices: category achievement (CA), perseverative

errors of Nelson (PEN), and difficulty of maintaining set (DMS).

CPT

The CPT was used to measure sustained attention or vigilance. We used the CPT-Identical Pairs version (CPT-IP) software, as described previously (Cornblatt *et al.*, 1988). A series of 4-digit stimuli were presented for a period of 50 ms, with an interstimulus interval (ISI) of 950 ms. Each complete task consisted of 150 trials of which 30 were target trials requiring a response. In this study, performance was measured by the signal detection index d-prime (d′), a measure of discriminability computed from "hits" and "false alarms."

N-back test

The N-back test was used to measure working memory. We used a working memory task software that requires subjects to update their mental set continually while responding to previously seen stimuli (i.e., numbers); the details thereof have been described previously (Callicott *et al.*, 2000; Callicott *et al.*, 2003). The stimulus duration was 0.4 s, and the ISI was 1.4 s; each test comprised 14 trials. The subjects responded to the stimuli by using the numeric keypad of the PC. In the present study, a 2-back condition was used, and performance was measured as the percentage of correct responses (accuracy, %).

Subjective measurements—Stanford Sleepiness Scale and adverse events

The Stanford Sleepiness Scale (SSS) is a 7-point, self-reporting measure with proven sensitivity in several studies (Hoddes *et al.*, 1973) and examines the level of alertness of an individual. The subjects were instructed to evaluate themselves on this scale before the initiation of the test battery at baseline and at 1 h and 4 h post-dosing. In addition, the adverse events spontaneously reported by the subjects or elicited by a nonleading question were recorded.

Statistical analyses

None of the outcome variables of the driving tests, cognitive tests, and subjective scales, except for BRT (harsh-braking test) and d′ (CPT), showed normal distribution. In order to compare the conditions following the administration of the 3 drugs, the differences between the baseline values and the 1-h and 4-h post-dosing values were analyzed. The non-normally distributed variables were analyzed by the nonparametric Friedman's χ^2 *r*-test. In the case of a significant treatment effect, a post-hoc analysis was performed by Wilcoxon signed-rank test (nonparametric) with Bonferroni's correction. The BRT and d′ data were normally distributed, and the differences between the baseline values and the 1-h and 4-h post-dosing values were analyzed using repeated measures analysis of variance (ANOVA). In the case of a significant treatment effect, a post-hoc analysis was done using the Bonferroni test for multiple comparisons. To clarify the correlations between driving performance and cognitive function, single regression analyses were conducted by the Spearman rank-order correlation (nonparametric); however, BRT and d′ were analyzed by the Pearson product-moment correlation. All statistical tests were conducted using SPSS version 11 for Windows (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Missing data

In the road-tracking test, three subjects administered amitriptyline failed to complete the test at 4 h post-dosing as they were sliding off the track. These subjects were not factored into the relevant statistical analyses. Because of technical malfunctions, three other subjects with incomplete data records were not factored into the statistical analyses of the N-back test. There were no missing data for the other driving and cognitive tests.

Driving performance

Summaries of results of the driving and cognitive tests are provided in Table 1 (a and b). Friedman's χ^2 *r*-test revealed a statistically significant effect of treatment on the differences between the baseline and 4-h post-dosing SDLP ($\chi^2 = 12.0$, $df = 2$, $p = 0.0025$) and DCV ($\chi^2 = 8.82$, $df = 2$, $p = 0.0121$) values. The post-hoc test demonstrated that the SDLP was significantly greater under the amitriptyline condition than under the other two conditions ($p < 0.05$ vs. placebo, $p < 0.01$ vs. paroxetine), and the DCV was significantly greater under the amitriptyline condition than under the paroxetine condition ($p < 0.01$). Repeated measures ANOVA showed no statistically significant differences in BRT among the three conditions. The results of the SDLP and DCV are

Table 1. Summary of the results of driving tests, cognitive tests, and subjective measurements in healthy male subjects enrolled in a crossover trial of paroxetine, amitriptyline and placebo ($N = 17$)

		Mean (SD)		
Measure	Test time	Placebo	Paroxetine 10 mg	Amitriptyline 25 mg
(a) Driving test				
SDLP* (cm)	Baseline	37.4 (7.81)	41.8 (10.68)	38.9 (10.84)
	1 h	37.2 (7.66)	38.9 (9.00)	38.9 (8.55)
	4 h	36.9 (8.45)	38.9 (10.11)	51.3 (12.67)**
DCV	Baseline	23.6 (10.11)	26.8 (10.50)	25.3 (8.10)
	1 h	24.4 (10.92)	28.5 (16.21)	26.8 (13.21)
	4 h	25.7 (12.67)	27.2 (9.46)	36.1 (19.16)***
BRT (ms)	Baseline	547.7 (42.76)	551.1 (69.40)	557.9 (58.30)
	1 h	546.1 (64.16)	542.3 (60.49)	557.8 (66.90)
	4 h	549.7 (55.61)	553.4 (48.75)	573.7 (52.72)
(b) Cognitive tests				
WCST				
CA	Baseline	6.1 (0.43)	5.8 (0.66)	5.9 (0.43)
	1 h	5.9 (0.56)	5.9 (0.33)	5.6 (0.80)
	4 h	5.9 (0.43)	5.9 (0.60)	5.5 (0.87)***
PEN	Baseline	0.4 (0.79)	0.9 (1.93)	1.1 (1.34)
	1 h	0.8 (2.19)	0.7 (1.10)	1.6 (2.74)
	4 h	0.6 (1.28)	0.5 (1.28)	1.1 (2.60)
DMS	Baseline	0.1 (0.24)	0.2 (0.56)	0.2 (0.39)
	1 h	0.1 (0.24)	0.1 (0.24)	0.4 (0.71)
	4 h	0.0 (0.0)	0.1 (0.24)	0.4 (0.61)
CPT (d')	Baseline	3.0 (0.87)	2.7 (0.91)	2.9 (0.80)
	1 h	3.1 (0.78)	3.1 (0.83)	3.0 (0.79)
	4 h	3.3 (0.69)	3.0 (0.92)	2.6 (0.89)***
N-back test* (accuracy, %)	Baseline	90.3 (19.93)	88.8 (16.98)	87.76 (12.35)
	1 h	91.8 (14.52)	86.7 (16.78)	86.7 (14.25)
	4 h	88.3 (14.72)	81.1 (17.85)	86.2 (16.45)
(c) Subjective measurement				
SSS	Baseline	1.9 (0.70)	1.7 (0.59)	1.9 (0.56)
	1 h	2.1 (0.66)	2.1 (0.70)	2.1 (0.78)
	4 h	2.2 (0.64)	2.3 (0.69)	4.6 (0.86)****

SDLP, Standard deviation of lateral position; DCV, Distance coefficient of variation; BRT, Brake reaction time; WCST, Wisconsin Card Sorting Test; CA, Category achievement; PEN, Perseverative errors of Nelson; DMS, Difficulty of maintaining set; CPT, Continuous Performance Test; SSS, Stanford Sleepiness Scale.0

*$N = 14$.

**$p < 0.01$ overall treatment effect between the three groups (difference between 4 h and baseline); ***$p < 0.05$ overall treatment effect between the three groups (difference between 4 h and baseline); ****$p < 0.001$ overall treatment effect between the three groups (difference between 4 h and baseline).

presented in Figures 1 and 2. No subject suffered from simulator sickness during the experiment.

Cognitive function

In the CPT, repeated measures ANOVA revealed a statistically significant effect of treatment on the difference between the baseline and 4-h post-dosing d' values ($F = 4.79$, $df = 2$, $p = 0.015$). The post-hoc test demonstrated that d' was significantly decreased under the amitriptyline condition when compared with the placebo condition ($p < 0.05$). The CPT results are presented in Figure 3. In the WCST, Friedman's χ^2 r-test revealed a statistically significant effect of treatment on the difference between baseline and 4-h post-dosing CA values ($\chi^2 = 6.54$, $df = 2$, $p = 0.038$); however, the post-hoc test did not show significant differences among the three groups. For the remaining cognitive measurements, no statistically significant effects of treatment were observed.

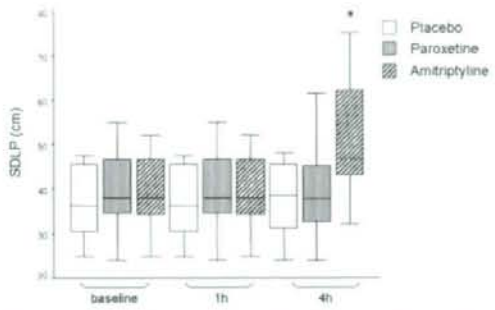

Figure 1. Box-and-whisker plot of the SDLP at baseline and at 1 h post dose and 4 h post-dosing in the crossover treatment with paroxetine, amitriptyline, and placebo ($N = 14$). Boxes indicate the interquartile ranges, with medians designated by the horizontal line. The differences between the baseline and the 4-h post-dosing values under the three conditions were compared. There was a significant effect of treatment ($^{*}p = 0.0025$). The post-hoc test demonstrated that the SDLP was significantly greater under the amitriptyline condition than under the placebo condition ($p < 0.05$) and the paroxetine condition ($p < 0.01$)

Subjective measurements

A summary of results of the SSS is shown in Table 1-c. Friedman's χ^2 *r*-test showed that there was a significant effect of treatment on the difference between the baseline and 4-h post-dosing SSS scores ($\chi^2 = 31.3$, $df = 2$, $p < 0.001$). Post-hoc tests clarified that alertness was significantly decreased under the amitriptyline condition when compared with the paroxetine ($p < 0.01$) and placebo ($p < 0.01$) conditions. A summary of adverse events is provided in Table 2.

Correlations among driving performance, cognitive function, and subjective assessments

Single regression analyses revealed significant correlations between driving performance and cognitive function. The significant correlations are outlined in Table 3.

DISCUSSION

The results of the present study demonstrated that 4 h after taking a single 25-mg dose of amitriptyline, there was significant impairment of DCV and of the established driving performance variable SDLP in the context of driving on crowded urban roads at relatively low speeds. Vigilance in the CPT and subjective somnolence in the SSS were also significantly impaired at 4 h after amitriptyline dosing. In contrast, acute doses of paroxetine or placebo did not significantly impair driving performance or cognitive function.

Although most of the present results are consistent with those of prior studies (Ramaekers, 2003; Ridout and Hindmarch, 2001; Ridout *et al.*, 2003; Wingen *et al.*, 2005), the present study was conducted from a different methodological viewpoint. The car-following performance is important with respect

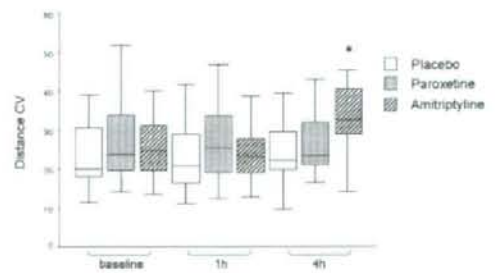

Figure 2. Box-and-whisker plot of the DCV at baseline and at 1 h and 4 h post-dosing in the crossover treatment with paroxetine, amitriptyline, and placebo ($N = 17$). Boxes indicate the interquartile ranges, with medians designated by the horizontal line. The four outlier values (1.5- to 3-fold of the interquartile range) and four extreme values (>3-fold of the interquartile range) have been omitted from the figure, but these values were included in the statistical analysis. The differences between the baseline and 4-h post-dosing values under the three conditions were compared. There was a significant effect of treatment ($^{*}p = 0.012$). The post-hoc test demonstrated that the DCV was significantly greater under the amitriptyline condition than under the paroxetine condition ($p < 0.01$)

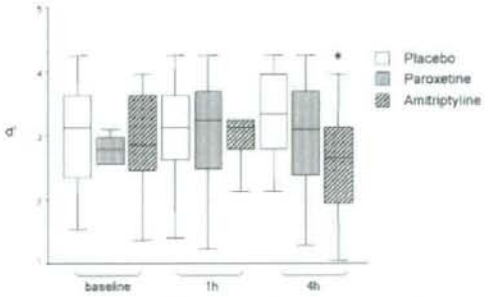

Figure 3. Box-and-whisker plot of the CPT (d') at baseline and at 1 h post dose and 4 h post dose of crossover treatment with paroxetine, amitriptyline, and placebo ($N = 17$). Boxes indicate the interquartile ranges, with medians designated by the horizontal line. The seven outlier values (1.5- to 3-fold of the interquartile range) and two extreme values (>3-fold of the interquartile range) have been omitted from the figure, but these values were included in the statistic analysis. The differences between the baseline and 4-h post-dosing values under the three conditions were compared. There was a significant effect of treatment ($^{*}p = 0.015$). The post-hoc test demonstrated that the d' was significantly decreased under the amitriptyline condition than under the placebo condition ($p < 0.05$)

Table 2. Adverse events in healthy male subjects enrolled in a crossover trial of paroxetine, amitriptyline and placebo. *N* (%) (*N* = 17)

Adverse event	Placebo	Paroxetine 10 mg	Amitriptyline 25 mg
Somnolence	0 (0)	2 (11.8)	16 (94.1)
Dizziness, light headedness	0 (0)	0 (0)	5 (29.4)
Stuffy head	1 (5.9)	1 (5.9)	11 (64.7)
Nausea	0 (0)	0 (0)	1 (5.9)
Dry mouth	0 (0)	0 (0)	3 (17.6)
Fatigue	0 (0)	0 (0)	5 (29.4)
Uncomfortable feeling in the head	0 (0)	0 (0)	1 (5.9)

to skills necessary for daily driving on crowded urban roads. The following distance is important for avoiding car crashes (Brookhuis *et al.*, 1994); however, it was hitherto difficult to measure the following distance in actual driving tests and the same setting was not investigated in previous simulator driving tests. Therefore, our simulator test may be considered complementary to actual driving tests. In addition, the results of the present 5-min simulator road-tracking test were similar to those of previous actual driving tests, which may require more time and higher expenditure.

The present simulator scenarios were different from actual driving tests in terms of course configuration and driving settings. Therefore, it is difficult to compare the parameters between simulator testing and actual driving. The gently winding road resulted in difficulties in stabilizing the vehicle in the center of the road, thereby yielding considerably higher SDLP values than actual driving tests, even under the placebo condition. The non-normal distributions of the driving variables could be attributed to the small sample size, complicated by the inability of some subjects to complete the task and by some outliers related to differences in the drug metabolizing capacities of subjects. Although the effects of antidepressants on the DCV were similar to those on the SDLP, no significant differences in BRT were observed among the three conditions. It was assumed that the other driving tasks were more complex than the harsh-braking task and might have therefore caused the significant differences. In the present study, there were no significant differences in executive function and working memory performance between baseline and post-dosing values. Although amitriptyline administration has been repeatedly associated with negative effects (Hindmarch *et al.*, 1983; Kerr *et al.*, 1996; Richardson *et al.*, 1994; van Laar *et al.*, 2002), the variables measured in the WCST and N-back test could be considered to have high SD values that may have potentially influenced the present outcome.

Driving skills comprise many basic cognitive and psychomotor elements, and the simultaneous application of these functions is required for safe driving. Regression analyses revealed that the negative effects of antidepressants on driving performance were associated with diminished sustained attention, executive impairment, and increased somnolence, although the low correlation coefficients warrant further investigations. Previous findings that are consistent with ours also show that somnolence or sedation is the most important cause of driving impairment in patients treated with antidepressants (Ramaekers, 2003).

Differences in the pharmacological properties of SSRIs and TCAs may provide a reasonable explanation for our results. Amitriptyline, unlike paroxetine, has strong antagonistic effects on cholinergic, adrenergic (α1), and histaminergic (H1) receptors, causing cognitive impairment, balance disturbance, and sedation, respectively. These common characteristics of TCAs may impair driving performance (Hindmarch *et al.*, 1983; Robbe and O'Hanlon, 1995; van Laar *et al.*, 1995; Wingen *et al.*, 2005). In the present study, amitriptyline did not significantly impair driving performance and cognitive function at 1 h post-dosing; this is not consistent with the previous results obtained using amitriptyline. However, most of the previous studies administered 25 mg amitriptyline 2 or 3 times daily. Although several studies showed impaired performance 1–2 h after a single administration of 25 mg or less amitriptyline (Bye *et al.*, 1978), the results obtained at the low doses varied with the tasks or subjects' ages (Crome and Newman, 1978; Kinirons *et al.*, 1993; Nathan *et al.*, 2000; Ogura *et al.*, 1983; Peck *et al.*, 1979; Tiller, 1990). The absence of amitriptyline effects at 1 h post-dosing could be chiefly due to the present tests employing single low doses. Furthermore, the low sensitivity of the driving simulator to the drug effects might also have contributed to the absence of amitriptyline effects at 1 h post-dosing.

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Table 3. Correlation between driving tests, cognitive tests, and subjective assessments

Measure	Driving test		
	SDLP (cm)	DCV	BRT (ms)
	r	*r*	*r*
Cognitive tests			
WCST			
CA	−0.23*	−0.17**	−0.053
PEN	0.13	0.21*	0.017
DMS	−0.012	0.20**	−0.092
CPT (d')	−0.28*	−0.20**	−0.094
N-back test (accuracy, %)	0.035	−0.067	0.019
Subjective measurement			
SSS	0.14	0.25*	0.14

SDLP, Standard deviation of lateral position; DCV, Distance coefficient of variation; BRT, Brake reaction time; WCST, Wisconsin Card Sorting Test; CA, Category achievement; PEN, Perseverative errors of Nelson; DMS, Difficulty of maintaining set; CPT, Continuous Performance Test; SSS, Stanford Sleepiness Scale.
*$p < 0.01$; **$p < 0.05$.

The present study has some potential limitations. First, participation was restricted to healthy adult volunteers. Neither elderly nor depressed patients were studied; their responses to antidepressant treatment could widely differ from those of healthy, younger adults. Second, we can extrapolate the results of our study only to patients receiving initial administration since our treatments were restricted to acute dosing. Third, the validity and sensitivity of the driving simulator need to be considered. A 5-min testing scenario may be inadequate for a behavioral test. In the harsh-breaking test, breaking to avoid hitting seven people crossing the road within 5 min might have alerted the subjects, thereby overcoming the drug-induced sedation. In the car-following test, subjects can choose different car-following distances under different conditions (Brookhuis *et al.*, 1994). The authors are aiming to improve the driving simulator and testing conditions in future studies to reflect real driving conditions in cooperation with Toyota Central R&D Labs., Inc. Finally, the authors' methodology could be useful to evaluate driving skills, particularly under hazardous conditions without real driving; however, it is necessary to significantly increase the sensitivity and reliability of the driving simulator. Since females constitute a major proportion of depressed patients, future investigations should include female subjects after adjusting for their menstrual cycles.

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Regular Article

Plasma amitriptyline level after acute administration, and driving performance in healthy volunteers

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Aims: Amitriptyline triggers the impairment of cognitive and motor functions and has been confirmed to have harmful effects on driving performance. Although interindividual differences in plasma concentration may cause variations in driving performance, the relationship between plasma amitriptyline concentration and its effect on driving performance has not been completely elucidated. Thus, the aim of the present study was to assess the influence of individual pharmacokinetic differences on driving performance and cognitive functions.

Methods: In this double-blinded study, 17 healthy male volunteers were given an acute, single, 25-mg dose of amitriptyline. The subjects were assigned three driving simulator tasks, three cognitive tasks, and the questionnaire of the Stanford Sleepiness Scale at the baseline and at 4 h after dosing. The plasma amitriptyline concentrations were measured on high-performance liquid chromatography.

Results: A significant positive correlation was observed between the plasma amitriptyline concentration and road-tracking performance ($r = 0.543$, $P < 0.05$). There was no significant correlation between the plasma amitriptyline concentration and other driving performance, cognitive functions, and subjective somnolence.

Conclusions: Amitriptyline produces a concentration-related impairment on road-tracking performance. Therapeutic monitoring of amitriptyline would be useful for predicting the difficulties involved while driving.

Key words: amitriptyline, antidepressants, automobile driving, cognition, drug monitoring.

INTERINDIVIDUAL DIFFERENCES IN drug responses occur even when the same dosage of a drug is prescribed to different individuals. Therapeutic drug monitoring (TDM) is one of the most valid tools utilized to minimize interindividual differences in drug responses. TDM enables a clinician to adjust the drug dosage and enhance efficacy and safety.[1] In the case of antidepressants, tricyclic antidepressants (TCA) are repeatedly recommended to be monitored for blood concentration[1–5] because these drugs have shown a fairly large interindividual variance in clinical response. The relationship between the blood TCA concentration and adverse effects, such as dropout rate, central nervous system toxicity, and cardiovascular toxicity has been reported.[4,6]

Among TCA, there is no consensus regarding the relationship between plasma amitriptyline concentration and therapeutic response, in contrast to that for imipramine, desipramine, and nortriptyline.[2,3] Previous studies reported different results regarding the relationship between plasma amitriptyline

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concentration and common adverse effects such as drowsiness and dry mouth. For example, although these adverse events were attributed to high plasma concentration of amitriptyline, correlation for low–moderate concentrations of amitriptyline was not observed.[7]

Epidemiological data indicate that TCA users are twice as likely to be involved in traffic accidents as compared to non-users.[8,9] Various studies have demonstrated the harmful effects of TCA on driving performance.[10] As for amitriptyline, impairment of road tracking performance and increase in brake reaction time have been reported.[11,12] Amitriptyline also has been linked to impairment of cognitive functions as well as driving performance. A single low dose of amitriptyline impaired cognitive functions as measured on cognitive tests such as auditory vigilance test, tapping test, arithmetic test, digit symbol substitution test, short term memory test, flicker-fusion test, and choice reaction time test.[13–19]

In our recent study we used simulator scenarios to examine car-following performance in the context of crowded urban roads and driving at relatively low speeds as well as other driving tasks routinely investigated in other previous studies. Furthermore, cognitive function was evaluated using the Wisconsin Card-Sorting Test (WCST), Continuous Performance Test (CPT), and N-back test. At 4 h after amitriptyline administration, road-tracking and car-following performance was significantly impaired, vigilance was reduced, and subjective somnolence was induced.[20]

Although the adverse effects of amitriptyline on driving performance and cognitive functions differ across individuals, to the best of our knowledge there have been no studies reported on the relationship between plasma amitriptyline concentration on the one hand, and driving performance and cognitive functions on the other. Considering the aforementioned factors, we examined the influence of individual pharmacokinetic differences on driving performance and cognitive functions using the same procedure as in our previous study.[20]

METHODS

Subjects

The sample consisted of 17 healthy male volunteers aged 30–42 years (mean ± SD, 35.8 ± 3.3 years). Based on health interviews and the Structured Clinical Interview for DSM-IV, the subjects were found to be free from any physical or psychiatric disorders and were not taking medication. All subjects had been in possession of a driving license for at least 10 years and had been driving a car daily (minimum, 5000 km/year). The study was approved by the ethics committee of the Nagoya University School of Medicine, and written informed consent was obtained from each subject prior to participation.

Procedure

All subjects were tested at approximately 09.30 hours using the Stanford Sleepiness Scale (SSS),[21] driving tests, and cognitive tests. The entire testing lasted approximately 1 h for each person. Following baseline assessment, the subjects were given capsules containing 25 mg amitriptyline in a double-blind manner. The dose of 25 mg was selected because it is a recommended starting dose in Japan, and also because the higher dose of amitriptyline might cause severe side-effects, possibly interrupting the experiments. Blood samples (10 mL) were collected 4 h after administration, because that is when maximum plasma drug concentration occurs.[22] The patients were subjected to all the aforementioned tests again after blood drawing. The blood samples were immediately centrifuged at 1700 *g*. for 10 min, and the plasma was frozen at −30°C. Plasma amitriptyline concentrations were determined on high-performance liquid chromatography, as described previously.[23] Five-point calibration curves were set up for the range 2–200 ng/mL. A linear response function was obtained, and the limit of quantification was 2 ng/mL. The interday coefficient of variation for 4 days for plasma amitriptyline at 20 ng/mL was 11.2%. The intraday coefficients of variation were 1.1–1.2% ($n = 2$). Amitriptyline has an active metabolite, nortriptyline. Both amitriptyline and nortriptyline undergo benzylic hydroxylation, and the hydroxylated nortriptyline metabolites are still active.[24] Jiang *et al.* reported that the plasma concentration of nortriptyline was considerably lower than that of amitriptyline after a single dose of amitriptyline.[22] The plasma concentrations of nortriptyline and its metabolites were not analyzed because the present study used only single low dosing and a short sampling interval after administration.

The subjects received substantial training in driving and cognitive tests 1 or 2 weeks prior to the first testing, and in order to minimize the learning effects

the subjects were trained until they reached the plateau level. Furthermore, the subjects were prohibited from consuming alcohol or beverages containing caffeine for 12 h before taking the tests and were requested to sleep adequately on the previous evening. On the test days the subjects were also prohibited from ingesting substances that may induce wakefulness, such as caffeine, supplement drinks, chewing gum, or candies because these substances could exert a stimulating effect on their performance. During the intervals between the test series, the subjects were assigned certain light tasks to prevent them from taking short naps.

Driving and cognitive tests

We used a driving simulator (Toyota Central R&D Labs, Nagakute, Japan) to examine three driving skills that appeared to be associated with the recent traffic accidents. The road-tracking test in the present study was based on a road-tracking test that was developed previously.[25,26] The subjects were instructed to drive at a constant speed of 100 km/h and stabilize their vehicles at the center of a gently winding road. The standard deviation of the lateral position (SDLP; cm), which indicates weaving, was considered a performance measure. The car-following test required the subjects to maintain a constant distance between the cars (targeted distance of 5 m) in the context of crowded urban roads driving at a speed of 40–60 km/h. The coefficient of variation (CV) was obtained by dividing the standard deviation of the car-following distance (m) between the cars by the mean value, and it was considered a performance measure.[27] Therefore, a smaller value of distance CV (DCV) would indicate a better performance. The harsh-braking test required the subjects to avoid crashing into the humanoid models that randomly ran on the road by harsh braking. The brake reaction time (BRT; ms) was considered a performance measure. Each test lasted for 5 min and the details have been described previously.[20]

The three cognitive tests were examined using a computer. In the WCST the performance was measured using the following indices: category achievement (CA), perseverative errors of Nelson (PEN), and difficulty of maintaining set (DMS).[28,29] In the CPT the performance was measured using the signal detection index d-prime (d'), which is a measure of discriminability computed from hits and false alarms.[30] In the N-back test a two-back condition was used, and the performance was measured as the percentage of correct responses (accuracy, %).[31,32]

Statistical analysis

None of the outcome variables of the driving tests, cognitive tests, and subjective scales, except BRT (harsh-braking test) and d' (CPT), had a normal distribution. To clarify the correlations between plasma amitriptyline concentration and percent change in performance, the Spearman rank-order correlation coefficients (non-parametric) were calculated. PEN and DMS were analyzed as difference not percent change, because their baseline values could be 0 and percent change could not be calculated. BRT and d' were analyzed using the Pearson product-moment correlation. In order to analyze the drug effect, the baseline values were compared to that obtained at 4 h after dosing using the Wilcoxon signed-rank test. A paired *t* test was used to analyze the BRT and d' data. All statistical tests were conducted using SPSS version 11 for Windows (SPSS Japan, Tokyo, Japan). Significance levels were set at 5% for all tests.

RESULTS

Correlations between plasma amitriptyline concentration and driving performance, cognitive function, and subjective assessments

The mean ± SD plasma amitriptyline concentration was 15.3 ± 6.4 ng/mL (range, 8.5–32.9 ng/mL). The relationships between the plasma amitriptyline concentration and driving performance, cognitive function, and subjective assessments are shown in Fig. 1. Data that indicate the coefficient of correlation of $-0.1 < r < 0.1$ are not shown. A significant correlation was observed between plasma amitriptyline concentration and percent change in SDLP (Fig. 1a). No significant correlations were detected between plasma amitriptyline concentration and the remaining driving, cognitive, and subjective variables (Fig. 1b–f). Percent change in CA, difference of PEN and percent change in SSS showed no significant correlations as follows: $r = -0.070$, $P = 0.789$ for CA, $r = 0.048$, $P = 0.855$ for PEN and $r = 0.035$, $P = 0.893$ for SSS; data not shown).

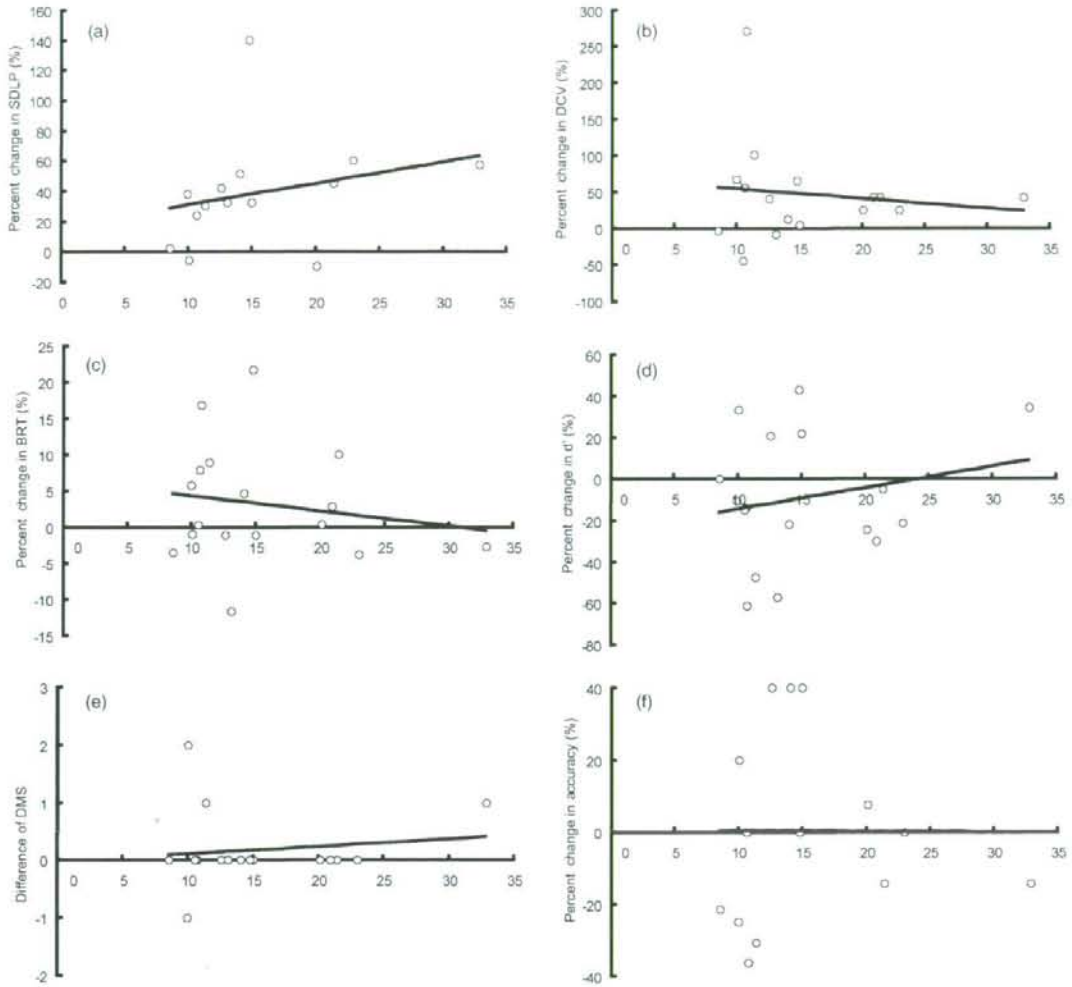

Figure 1. Relationship between plasma amitriptyline concentration and percent changes in the variables of driving performance, cognitive functions, and subjective somnolence. (Difference rather than percent change was used for (e) difficulty of maintaining set [DMS], because the baseline values of DMS can be 0 and hence, percent changes cannot be calculated.) (a) Percent change in standard deviation of the lateral position (SDLP; $r = 0.543$, $P = 0.045$); (b) percent change in distance coefficient of variation (DCV; $r = -0.110$, $P = 0.673$); (c) percent change in brake reaction time (BRT; $r = -0.163$, $P = 0.532$); (d) percent change in signal detection index d-prime (d') in the Continuous Performance Test ($r = 0.209$, $P = 0.420$); (e) difference of DMS in the Wisconsin Card-Sorting Test ($r = 0.132$, $P = 0.614$); (f) percent change in accuracy in the N-back test ($r = 0.260$, $P = 0.370$). Due to non-completion of the assigned task and technical malfunctions, three subjects were excluded from statistical analyses for SDLP and N-back test.

Effects of amitriptyline on driving performance, cognitive function, and subjective assessments

At 4 h after receiving the single dose of 25 mg amitriptyline, SDLP ($P = 0.003$), DCV ($P = 0.006$), CA ($P = 0.035$), and SSS score ($P = 0.0002$) were significantly impaired. The effect of amitriptyline on the remaining variables was not statistically significant. These data have been reported in our previous study.[20]

DISCUSSION

The present results demonstrated a significant linear correlation between plasma amitriptyline concentration and percent change in SDLP. Baseline SDLP was 38.9 ± 10.8 cm, and at 4 h it increased to 51.3 ± 12.7 cm. This increase of lateral swerving might lead to traffic accidents. The plasma amitriptyline concentration, however, did not show a significant relationship with (i) other driving performance parameters of DCV and BRT; (ii) cognitive functions measured using the WCST, CPT, and N-back test; or (iii) subjective somnolence, determined using the SSS.

In a previous study imipramine had a detrimental effect on driving performance measured as SDLP and caused slight cognitive impairment as assessed on a memory scanning test.[33] This memory test indicated that the plasma drug concentration significantly correlated with reaction time change but not with SDLP change. The present study found a significant correlation between plasma concentration of amitriptyline after a single dose and driving performance measured as SDLP. Amitriptyline may have a concentration-dependent detrimental effect on road-tracking ability. Therapeutic monitoring of amitriptyline would be useful for predicting the difficulties encountered while driving. The present results and those of the van Laar *et al.* study[33] do not agree, although both these studies used TCA. The methodological differences between the two studies might contribute to the discrepancy.

A previous review demonstrated that somnolence or sedation is the most important cause of driving impairment in patients treated with antidepressants.[10] In our previous simulator study we also confirmed a weak but significant association between the detrimental effects of antidepressants on driving performance and increased subjective somnolence.[20] In the present study an acute dose of 25 mg amitriptyline strongly increased the SSS scores, but no significant correlation was observed between plasma amitriptyline concentration and percent change in SSS scores. These values might be influenced by individual pharmacodynamic differences rather than individual pharmacokinetic differences. The same logic may be applied to the absence of correlations between plasma amitriptyline concentration and DCV and CA (WCST); therefore, further investigations should be conducted in this regard.

Several studies indicate cognitive impairments in major depression patients.[34–36] Richardson *et al.* reported that amitriptyline and fluoxetine showed equal clinical improvement but patients receiving amitriptyline did not perform as well on the verbal learning task.[37] The present results indicate that TCA including amitriptyline might affect recovered cognitive function, even though clinical depressive symptoms are successfully treated.

The present study has several limitations. First, it used a single, low dose of amitriptyline. Therefore, we could not investigate the steady state condition, in which amitriptyline and its active metabolites exert their influence. Second, the participants were limited to healthy adult male volunteers; therefore, women who are prone to develop depression and the elderly should be included in future studies. Third, the validity and sensitivity of the driving simulator used in the present study should be considered. Finally, we found a significant linear correlation between plasma amitriptyline concentration and percent change in SDLP, but it is necessary to investigate this relationship under clinical therapeutic dose and steady-state conditions.

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