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

Kunihiro Iwamoto, MD,1 Yukiko Kawamura, MS,2 Masahiro Takahashi, MD,1 Yuji Uchiyama, PhD,2 Kazutoshi Ebe, ME,3 Keizo Yoshida, MD, PhD,1,* Tetsuya Iidaka, MD, PhD,1 Yukihiro Noda, PhD2 and Norio Ozaki, MD, PhD1
1Department of Psychiatry, Nagoya University, Graduate School of Medicine, 2Meijyo University, Graduate School of Pharmacy, Division of Clinical Science and Neuropsychopharmacology and 3Toyota Central R&D Labs., Aichi, Japan

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.
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).
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. study33 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.29 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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REFERENCES

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32 Callcott JH, Egan MF, Mattay VS et al. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively...


