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CHAPTER 5

PLACEBO- AND AMITRIPYLME-CONTROLLED EVALUATION OF CENTRAL NERVOUS SYSTEM EFFECTS OF THE NK₁ RECEPTOR ANTAGONIST APREPITANT AND INTRAVENOUS ALCOHOL INFUSION AT PSEUDO-STEADY STATE


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ABSTRACT

Recent interest in NK₁ receptor antagonists has focused on a potential role in the treatment of drug addiction and substance abuse. In the present study, the potential for interactions between the NK₁ receptor antagonist aprepitant and alcohol, given as an infusion at a target level of 0.65 g/L, was evaluated. Amitriptyline was included as positive control to provide an impression of the profile of central nervous system (CNS) effects. In a double-blind, randomized, placebo- and amitriptyline-controlled study, the pharmacokinetics and CNS effects of aprepitant and alcohol were investigated in 16 healthy volunteers. Cognitive and psychomotor function tests included the visual verbal learning test (VVLT), Bond and Lader visual analogue scales (VAS), digit symbol substitution test (DSST), visual pattern recognition, binary choice reaction time, critical flicker fusion (CFF), body sway, finger tapping and adaptive tracking. Alcohol impaired finger tapping and body sway. Amitriptyline impaired DSST performance, VAS alertness, CFF, body sway, finger tapping and adaptive tracking. No impairments were found after administration of aprepitant. Co-administration of aprepitant with alcohol was generally well tolerated and did not cause significant additive CNS effects, compared with alcohol alone. Therefore, our study found no indications for clinically relevant interactions between aprepitant and alcohol.
INTRODUCTION

The peptide neurotransmitter substance P and its preferred receptor, the neurokinin 1 (NK1) receptor have been the focus of several different drug development programs. Recently, interest in NK1 receptor antagonists has focused on a potential role in the treatment of drug addiction and substance abuse disorders. Substance P may play a role in addiction-related behavior by acting directly on NK1 receptors in brain areas associated with drug reward, such as the nucleus accumbens and ventral pallidum, and on dopaminergic neurons in the ventral tegmental area, but also by influencing other neurotransmitters such as serotonin, acetylcholine and noradrenalin. Studies in animals have demonstrated that pharmacological blockade of NK1 receptors dose-dependently suppresses alcohol intake and stress-induced reinstatement of alcohol seeking behavior. Also, the rewarding effects of opiates (but not cocaine) are absent in NK1 receptor knockout mice and in mice with bilateral ablation of NK1 receptor-expressing neurons in the amygdala. A recent case-control association study identified two haplotypes and a single nucleotide polymorphism (SNP) in the NK1 receptor gene (NK1R) that were significantly associated with the development of alcohol dependence. Furthermore, a recent clinical trial with the NK1 receptor antagonist LY686017 in detoxified alcoholic inpatients demonstrated suppression of spontaneous alcohol cravings and improved overall well-being.

The present study was performed to evaluate possible interactions between the NK1 receptor antagonist aprepitant and alcohol. Pharmacokinetic interactions are not expected because aprepitant is metabolized primarily by CYP3A4, whereas alcohol is metabolized by a pathway that involves alcohol dehydrogenase, catalase and CYP2E1. However, pharmacodynamic interactions are theoretically possible as both compounds are centrally active and may influence several neurotransmitters, including dopamine. A battery of quantitative tests, sensitive to the central effects of various compounds, including alcohol, was used to evaluate pharmacodynamic central nervous system (CNS) effects. Similar to the phase III trials with aprepitant for the indication of major depressive disorder, an oral dose of 160 mg of aprepitant had been chosen for this study, because this dose was generally well tolerated in the depression program and was expected to result in high occupancy of central NK1 receptors. Positron emission tomography (PET) using [18F]SPA-RQ in healthy volunteers has demonstrated that daily doses of 100 mg aprepitant or higher achieve high levels (>90%) of NK1 receptor occupancy in the striatum. The effects of co-administration of aprepitant and alcohol were primarily compared with those of alcohol alone and aprepitant alone. At the time of study execution, no other studies evaluating NK1 receptor antagonists with this
pharmacodynamic test battery were available. As a consequence, no a priori estimation of effect size of aprepitant with or without alcohol could be made. To set a clinical benchmark for the effect size of CNS effects of co-administration of aprepitant and alcohol, we included amitriptyline as a comparator drug. Amitriptyline shows a wide range of significant CNS effects in healthy volunteers, which have been well characterized previously using this pharmacodynamic test battery. 

**METHODS**

*Study design*

Sixteen healthy male or female volunteers, between 18 and 55 years of age were planned to participate in a double-blind, randomized, placebo- and active comparator-controlled, triple-dummy, four treatment, two-period crossover study to investigate the psychomotor and cognitive effects of aprepitant and ethanol in healthy volunteers. The study was approved by the medical ethics committee of the Leiden University Medical Center. Prior to medical screening, all volunteers gave written informed consent. Medical screening included a medical history, physical examination, urinalysis, routine haematology and chemistry and 12-lead electrocardiography (ECG). All volunteers underwent training sessions for the pharmacodynamic tests in order to minimize possible learning effects.

This study was designed primarily to compare the effects of co-administration of aprepitant and alcohol with those of alcohol alone and aprepitant alone. To optimize the likelihood of detecting possible pharmacodynamic effects, aprepitant was administered daily for 7 days, after which plasma concentrations of aprepitant can be expected to be maximal (Merck & Co., data on file). As stated, amitriptyline was included in this study as an pharmacodynamic comparator, which is expected to exert its maximum tolerable effects after a single dose.

The study consisted of study periods of 10 days (see Figure 1). On day 1, all volunteers were administered 50 mg amitriptyline (or placebo capsules) and a placebo-ethanol infusion (consisting of a 5% glucose solution). On day 2 and 3, all volunteers were administered placebo capsules to allow a complete washout of amitriptyline. On days 4 to 10, all volunteers took 160 mg aprepitant once daily as nanoparticle capsules (or placebo capsules). On day 10, all volunteers received an active alcohol infusion (5% alcohol in a 5% glucose solution, see below for details). Psychomotor and cognitive testing was performed on day 1, 9 and 10 (see Figure 2). This study design minimizes carry-over effects of amitriptyline administration at day 1 on the pharmacodynamic measurements on days 9 and 10, as the half life of amitriptyline is roughly 20 hours. On days 2, 4, 6 and 8, the volunteers reported to the clinic for administration of study medication. On
days 3, 5 and 7, the volunteers administered study medication at home, which was confirmed by telephone. Each volunteer participated in two study periods in a randomized, blinded crossover fashion (see Figure 1). Both study periods were separated by a washout period of at least 14 days.

**FIGURE 1**  
Study design. Active treatments are indicated in bold.

**FIGURE 2**  
Schedule of pharmacokinetic and pharmacodynamic tests performed on days 1, 9 and 10 of both study periods.  

- Pharmacokinetic (PK) sampling includes blood sampling for aprepitant concentration analysis on study days 9 and 10, and breath sampling for alcohol concentration analysis on study day 1 and 10.  
- Psychomotor tests include the adaptive tracking test, critical flicker fusion, finger tapping, and body sway.  
- Amitriptyline (or placebo) on study day 1, aprepitant (or placebo) on study day 9 and 10.  
- Alcohol infusion on study day 10 and placebo infusion on day 1.
This rather complex study design enables, after combining both study periods, analysis of the following comparisons:

- On day 1, single doses of amitriptyline (or placebo) are administered, followed by pharmacokinetic and pharmacodynamic measurements. These data enable analysis of the effects of single oral doses of amitriptyline \((n = 16)\) compared with placebo \((n = 16)\).

- On days 4-9, single daily doses of aprepitant (or placebo) are administered. On day 9, pharmacokinetic and pharmacodynamic measurements are performed. These data enable analysis of the effects of aprepitant \((n = 16)\) compared with placebo \((n = 16)\).

- On day 1, a placebo-ethanol infusion (consisting of a 5% glucose solution) and placebo capsules (or amitriptyline) are administered, followed by pharmacokinetic and pharmacodynamic measurements. On day 10, an alcohol infusion and placebo capsules (or aprepitant) are administered, followed by pharmacokinetic and pharmacodynamic measurements. These data enable analysis of the effects of alcohol infusion \((n = 16)\) compared with placebo infusion \((n = 16)\), although it is recognized that the estimated effects are confounded with day.

- On day 10, an alcohol infusion and aprepitant (or placebo capsules) are administered, followed by pharmacokinetic and pharmacodynamic measurements. These data enable analysis of co-administration of aprepitant and alcohol \((n = 16)\), compared with co-administration of placebo and alcohol \((n = 16)\).

**Alcohol infusion paradigm**

The procedure for attaining pseudo-steady state alcohol levels was based on the method of Hartmann et al\(^{18}\) and performed as described earlier\(^{19-21}\). In brief, alcohol (ethanol 5% w/v solution in 5% glucose) was administered intravenously to achieve a target blood alcohol concentration of 0.65 g/L, beginning 2½ hours after administration of aprepitant (or placebo) and ending 6½ hours after study drug administration in order to coincide with the expected maximal plasma concentration of aprepitant \((t_{\text{max}}\) of the marketed 80 mg and 125 mg capsules is roughly 4 hours)\(^{22}\). Breath alcohol concentrations were determined at 0, 60, 90, 150, 180, 210 and 300 minutes after start of the alcohol infusion using a calibrated hand-held Alco-Sensor \(^{\text{iv}}\) Intoximeter (Honac, Apeldoorn, the Netherlands), which has a limit of quantification \((\text{LOQ})\) of 0.01 g/L. Alcohol infusion was performed at a constant rate for the first hour, followed by a slower constant rate over the next 3 hours to maintain the target level.

Rates of infusion were set individually, based on measured alcohol kinetics in each volunteer during a separate alcohol infusion, after inclusion in the study.
but prior to the first study period. During this pre-study infusion, 50 gram of alcohol was administered intravenously over 1 hour (500 mL of 100 g/L ethanol solution in 5% glucose). Serum alcohol and breath alcohol concentrations were determined prior to infusion and at 30, 55, 75, 90, 120, 180, 240, 300 and 360 minutes after start of the alcohol infusion. Individual pharmacokinetic parameters were calculated by fitting the serum alcohol concentrations to a two-compartment open model with Michaelis-Menten kinetics, derived from previous studies\textsuperscript{18–20}. Population parameters were used as priors in a Bayesian nonlinear regression analysis to generate pharmacokinetic parameters of individual infusion regimes. The regime that approaches and stays at 0.65 g/L was applied on subsequent alcohol infusions. Pseudo-steady state alcohol levels were attained after approximately 90 minutes. To avoid an overshoot in the alcohol levels, the infusion of alcohol was terminated whenever the level of 1.00 g/L was reached. Pharmacokinetic modeling and simulation was performed using NONMEM (software version V, University of California, San Francisco, USA).

**Aprepitant pharmacokinetics**

Venous blood samples for aprepitant concentration analysis were collected prior to study drug administration on days 1, 9 and 10 and at \( \frac{1}{2}, \frac{3}{2}, 4, 5, \frac{5}{2}, 6 \) and \( 7\frac{1}{2} \) hours after study drug administration of aprepitant (or placebo) on days 9 and 10 (see Figure 2). The concentration of aprepitant in plasma samples was determined using HPLC-MS/MS with a lower limit of quantification (LLQ) of 10 ng/mL, using a previously reported method\textsuperscript{23,24}.

**Safety monitoring**

Evaluation of adverse events, 12-lead electrocardiograms (ECG), blood pressure, heart rate, body temperature, urinalysis and blood sampling for haematology and chemistry was performed at regular time points during the study.

**Pharmacodynamic testing**

Volunteers were tested on days 1, 9 and 10 of each study period individually in a quiet room with ambient illumination. Cognitive function tests included the visual verbal learning test (VVLT) and Bond and Lader visual analogue scales (VAS), which were performed roughly 2\( \frac{1}{2} \) hours after study drug administration (see Figure 2), and the digit symbol substitution test (DSST), visual pattern recognition with immediate and delayed recall and binary choice reaction time, which were performed roughly 4 hours after study drug administration (see Figure 2). Psychomotor function tests were performed prior to dose administration and at \( \frac{1}{2}, 3, 4\frac{1}{2}, 6, 7\frac{1}{2} \) and 9 hours after drug administration (see Figure
2) and included critical flicker fusion (cFF), body sway, finger tapping and adaptive tracking. The primary endpoint of this study was the digit symbol substitution test (DSST). The visual verbal learning test (VVLT), Bond and Lader visual analogue scales (VAS), pattern recognition, binary choice reaction time, critical flicker fusion (cFF), finger tapping, adaptive tracking, and body sway were secondary endpoints. Change from baseline critical flicker fusion (cFF), finger tapping, adaptive tracking and body sway were exploratory endpoints.

**Digit-symbol substitution test**

During the digit-symbol substitution test (DSST)\(^{25}\), the volunteer is asked to assign symbols to random digits using a substitution key that is presented on the worksheet. Each digit-symbol association constitutes one response and volunteers are instructed to complete as many responses as possible within 90 seconds. The number of correct substitutions is analyzed.

**Visual verbal learning test**

During the visual verbal learning test (VVLT)\(^{26}\), three trials of 30 words are presented on a computer screen in the same sequence. The volunteer is requested to reproduce as many words as possible at the ending of each trial (immediate recall) and after 30 minutes (delayed recall). The number of correctly reproduced words is analyzed for each trial. Also, a recognition test is performed, consisting of 15 previously presented words and 15 new words, in which the volunteer has to indicate recognition of the word (delayed recognition) as quickly as possible. Response time (msec) and the number of correctly recognized words are analyzed.

**Visual pattern recognition**

A trial of 14 abstract visual patterns is presented on a computer screen for a duration of 3 seconds per pattern. A recognition test is performed, consisting of the same 14 previously presented patterns along with new patterns, in which the volunteer has to indicate recognition of the pattern as quickly as possible at the ending of the trial (immediate recall) and after 30 minutes (delayed recall). Response time (msec) and the number of correctly recognized patterns are analyzed.

**Binary choice reaction time**

Choice reaction time\(^{27}\) is measured by displaying either a red or green block on either the left side or right side of a computer screen in random order. The volunteer reacts by pushing a button on either side of the keyboard, corresponding to
the position of the colored block on the screen. Sixty stimuli are presented and response time (msec) and the number of correct responses are analyzed.

**Visual analogue scales**

Subjective effects were quantified using a Dutch translation of the visual analogue scales (VAS), originally described by Norris\(^28\), to derive three composite factors corresponding to alertness, mood (contentedness) and calmness, as described by Bond & Lader\(^29\).

**Critical flicker fusion**

An intermittent light source is used with an increasing and decreasing frequency. The frequency at which the flickering light is perceived as a steady light source is termed the critical flicker fusion (CFF) threshold, which is a measure for CNS activation\(^30\). Volunteers are requested to respond by pressing a button at the moment they see fusion of flickering (when frequency is increased) or when the light starts to flicker (when frequency is decreased). Average response (threshold frequency in Hz) during four sequences is calculated.

**Body sway**

Postural stability in the sagittal plane was measured with an apparatus similar to the Wright ataxiameter\(^31\), using a string attached to the waist of the volunteer. Movements over a period of two minutes, while standing still with eyes closed, were integrated and expressed as mm sway.

**Finger tapping**

The finger tapping test was adapted from the Halstead-Reitan test battery\(^32\) to evaluate motor activation and fluency. The volunteer is instructed to rest the wrist of the dominant hand on a table and to tap as quickly as possible with the index finger onto the space bar of a key board. The mean tapping rate is used for statistical analysis.

**Adaptive tracking**

To evaluate visuo-motor coordination, the adaptive tracking task was performed as described previously\(^33\), using customized equipment and software developed by K.W. Hobbs (Hertfordshire, UK). Adaptive tracking is a pursuit tracking task in which a circle moves randomly over a computer screen and the volunteer must try to keep a dot inside the moving circle using a joystick. If this effort is successful, the speed of the moving circle is increased and if the effort is unsuccessful, the speed is reduced. Performance was scored over a fixed period of 10 minutes.
**Statistical analysis**

Evaluation of the numbers of correct substitutions from the digit symbol substitution test (DSST) was performed using an analysis of variance (ANOVA) model appropriate for a two-period crossover design, with factors for sequence, subject-within-sequence, period, treatment and within subject error. A two-sided 90% confidence interval (equivalent to a one-sided 95% confidence interval) for the true mean treatment difference was computed from the ANOVA using the mean squared error and referencing a t-distribution. Data from day 1 were used for comparison of amitriptyline and placebo. Data from day 9 were used for comparison of aprepitant and placebo. Data from day 10 were used for comparison of alcohol and co-administration of aprepitant and alcohol. An ANOVA with factors for subjects and treatment was used to compare alcohol (data from day 10) and placebo for alcohol (data from day 1), although the estimated alcohol effect was confounded with day. VVLT results, visual pattern recognition with immediate and delayed recall, binary choice reaction time and visual analogue scales were each analyzed with the same methods used for the DSST. It was determined post-hoc that due to observed statistically significant differences between treatment groups at baseline, critical flicker fusion (CFF), finger tapping, adaptive tracking and body sway should be baseline adjusted. The change from baseline values were also analyzed with the same methods used for the DSST, with the addition of factors for hour and the interaction of treatment-by-hour to the ANOVA model. The measurements performed 1½ hours after study drug administration were not included in the change from baseline analyses, because this time point was prior to alcohol infusion. For body sway data, the fold change from baseline was calculated, because the data were distributed as log-normal. All tests were performed at a significance level of 0.05 (two-tailed). No corrections for multiple comparisons were made.

In addition, to get an impression of possible effects of alcohol infusion on the pharmacokinetics of aprepitant after multiple doses, the repeated measured aprepitant plasma concentrations after co-administration of alcohol and aprepitant on day 10, were compared to those after administration of aprepitant alone on day 9, using a mixed model analysis of variance with treatment, time and treatment by time as fixed factors and subject, subject by treatment and subject by time as random factors. Because the alcohol infusion started 2½ hours after administration of aprepitant (or placebo), only the blood samples taken after t = 2½ hours were included in the analysis. Furthermore, because on days 9 and 10, aprepitant had already been administered for 6 and 7 days, respectively, the pre-values (i.e. the plasma concentration measurements before aprepitant administration on days 9 and 10, respectively) were included in the model as a covariate.
It is recognized that, in this analysis, treatments are sequential and not randomized. Data were natural log-transformed prior to analysis and the log scale estimates of the treatment difference (plasma concentration of aprepitant with or without alcohol) and 95% confidence interval for the treatment difference were exponentiated to obtain the geometric mean ratio and 95% confidence interval.

RESULTS

Subjects
A total of 17 healthy volunteers (9 males and 8 females) were included and randomized. Participants had a mean age of 27 years (range 18-53), weight of 77.1 kg (range 52.6-95) and body mass index of 24.9 kg/m² (range 19.8-30.2). One volunteer was withdrawn after completing the first study period, because of phlebitis on both arms on day 11. This volunteer was randomized to receive treatments B and C and was replaced by a new volunteer who completed both study periods. Safety data from all 17 volunteers is reported below. Statistical analysis was subsequently performed on all pharmacokinetic and pharmacodynamic data sets of all volunteers who completed both study periods (i.e. \( n = 16 \)).

Clinical observations
Adverse events were generally mild and occasionally moderate in severity. No serious adverse events occurred during the study. The most frequently reported adverse events after administration of aprepitant were tiredness or somnolence (7), headache (2) and dizziness (2). The most frequently reported adverse events after administration of amitriptyline were tiredness or somnolence (15) and dizziness (2). The most frequently reported adverse events after alcohol infusion were feeling drunk (13), tiredness or somnolence (6), altered taste (2) and local infusion reactions (which generally consisted of pain at the infusion site) (9). The combination of aprepitant with alcohol infusion did not affect the frequency or intensity of feeling drunk and local infusion reactions. The most frequently reported adverse events after co-administration of aprepitant and alcohol were feeling drunk (13), local infusion reactions (10), tiredness or somnolence (9), headache (3), nausea (2), altered taste (2) and dry mouth (2). There were no clinically relevant changes in heart rate, blood pressure, haematology, biochemistry, urinalysis or ECG.

Pharmacokinetics of alcohol
Following intravenous infusion, breath alcohol levels increased rapidly and remained fairly constant at the target level all over the time of infusion (see Figure 3).
**Figure 3**  Breath alcohol levels after intravenous alcohol infusion starting at $t = 2\frac{1}{2}$ hours and continuing until $t = 6\frac{1}{2}$ hours on day 10, in combination with oral administration (at $t = 0$ hours) of aprepitant (open circles) or placebo (closed circles). Means are presented with standard deviations as error bars.

**Figure 4**  Plasma levels of aprepitant after oral administration at $t = 0$ hours, either alone on day 9 (closed circles) or in combination with alcohol infusion on day 10 (open circles), starting at $t = 2\frac{1}{2}$ hours and ending at $t = 6\frac{1}{2}$ hours. Means are presented with standard deviations as error bars.
Pharmacokinetics of aprepitant
As expected, plasma concentrations of aprepitant during study days 9 and 10 were generally quite stable, showing only a small increase at 3.5 to 4 hours after dose administration (see Figure 4), consistent with its $t_{\text{max}}$.

Pharmacokinetics of co-administration of alcohol and aprepitant
Plasma concentrations of aprepitant (see Figure 4) were higher when administered alone on day 9, compared with co-administration of alcohol on day 10 (estimate of difference in mean time-profile in percents was 11.3%; 95% confidence interval 3.9/18.2%; $p = 0.0065$).

Pharmacodynamics of alcohol
No statistically significant differences in the results of DSSST, binary choice reaction time or any of the visual analogue scales were observed, as demonstrated in Table 1. Despite a small decrease in immediate recall after the first and third trial ($p = 0.049$ and $p = 0.026$, respectively) and shorter reaction time (for incorrect answers) for word recognition ($p = 0.012$), no consistent effects of alcohol on VVLT performance was observed. Also, despite a shorter reaction time (for incorrect answers) for immediate recognition ($p = 0.042$), no consistent effects of alcohol administration on visual pattern recognition were observed.

As demonstrated in Table 2, body sway and finger tapping were significantly impaired ($p = 0.029$ or lower), whereas critical flicker fusion did not demonstrate any clear effect of alcohol administration compared to placebo. Adaptive tracking performance was significantly decreased at 7.5 hours postdose ($p = 0.012$), while decreases at 4.5 hours and 6 hours approached (but failed to reach) significance level.

Pharmacodynamics of amitriptyline
As demonstrated in Table 1, amitriptyline significantly decreased DSSST performance compared to placebo ($p = 0.008$). Despite a small decrease in immediate recall (numbers correct) after the third trial ($p = 0.014$), no consistent effects of amitriptyline on VVLT performance were observed. Visual pattern recognition and binary choice reaction time remained unaffected. VAS alertness was significantly decreased ($p = 0.005$), but no differences were found in any of the other visual analogue scales.

As demonstrated in Table 2, critical flicker fusion, body sway, finger tapping and adaptive tracking were significantly reduced after administration of amitriptyline compared to placebo ($p = 0.044$ and lower).
<table>
<thead>
<tr>
<th>Test</th>
<th>Alcohol versus placebo</th>
<th>Amitriptyline versus placebo</th>
<th>Aprepitant versus placebo</th>
<th>Co-administration of alcohol and aripiprazole versus alcohol alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference (90% CI)</td>
<td>p-value</td>
<td>Difference (90% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>dsST Number (correct)</td>
<td>-0.75 (-5.75/4.25)</td>
<td>0.382</td>
<td>-0.94 (-7.21/5.27)</td>
<td>0.333</td>
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<tr>
<td>dsST Immediate recall</td>
<td>-1.81 (-3.30/0.38)</td>
<td>0.128</td>
<td>-1.06 (-2.67/0.50)</td>
<td>0.240</td>
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<td>dsST Immediate recall 2nd trial</td>
<td>-2.06 (-3.32/0.60)</td>
<td>0.026</td>
<td>-2.00 (-2.81/0.81)</td>
<td>0.073</td>
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<td>dsST Delayed recall</td>
<td>-1.37 (-3.10/0.35)</td>
<td>0.182</td>
<td>-2.00 (-2.81/0.81)</td>
<td>0.073</td>
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<td>Word recognition</td>
<td>-0.05 (-1.41/1.01)</td>
<td>0.292</td>
<td>-2.00 (-2.81/0.81)</td>
<td>0.073</td>
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<td>Word Number (correct)</td>
<td>-1.89 (-4.40/0.87)</td>
<td>0.124</td>
<td>-1.63 (-3.55/0.24)</td>
<td>0.058</td>
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<td>Word Immediate recall (correct)</td>
<td>-105 (-22.70/12.41)</td>
<td>0.012</td>
<td>-2.00 (-2.81/0.81)</td>
<td>0.073</td>
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<td>Word Immediate recall (incorrect)</td>
<td>0.72 (-0.01/1.45)</td>
<td>0.104</td>
<td>0.42 (-0.64/1.47)</td>
<td>0.486</td>
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<td>Pattern recognition (immediate)</td>
<td>-2.15 (-4.81/0.74)</td>
<td>0.110</td>
<td>154 (-0.12/3.45)</td>
<td>0.122</td>
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<td>Pattern Number (correct)</td>
<td>-0.06 (-1.09/0.97)</td>
<td>0.861</td>
<td>-0.01 (-0.35/0.30)</td>
<td>0.994</td>
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<td>Pattern Reaction time (correct)</td>
<td>-7.82 (-13.14/18.60)</td>
<td>0.014</td>
<td>9.71 (-0.15/19.69)</td>
<td>0.030</td>
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<td>Pattern Reaction time (incorrect)</td>
<td>1.19 (-2.74/5.10)</td>
<td>0.036</td>
<td>3.39 (-0.39/7.16)</td>
<td>0.068</td>
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<td>Pattern Reaction time (incorrect)</td>
<td>-4.10 (-14.97/6.77)</td>
<td>0.194</td>
<td>4.10 (-14.97/6.77)</td>
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<td>Visual Factor 1 (differences)</td>
<td>-0.19 (-1.49/1.11)</td>
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<td>-0.50 (-2.10/1.10)</td>
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<td>Visual Factor 2 (sensitivities)</td>
<td>-10.37 (-17.70/1.93)</td>
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<td>Visual Factor 3 (analogy)</td>
<td>8.35 (-3.75/16.20)</td>
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<td>9.15 (-3.56/18.26)</td>
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<td>Visual Factor 4 (sensitivities)</td>
<td>0.49 (-0.52/1.43)</td>
<td>0.285</td>
<td>2.25 (-0.75/3.23)</td>
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Note: All results are expressed as differences in treatment means (with 90% confidence intervals and p-values). Statistically significant results are indicated in bold.
<table>
<thead>
<tr>
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<td>Difference (90% CI)</td>
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<td>p-value</td>
</tr>
<tr>
<td>Critical</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>flicker fusion</td>
<td>3 hours</td>
<td>-0.59 (-1.32/0.13)</td>
<td>0.176</td>
<td>-0.12 (-1.07/0.83)</td>
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<td>4.5 hours</td>
<td>-0.43 (-1.16/0.29)</td>
<td>0.322</td>
<td>-1.18 (-2.03/-0.33)</td>
</tr>
<tr>
<td></td>
<td>6 hours</td>
<td>-0.29 (-1.01/0.43)</td>
<td>0.510</td>
<td>-1.36 (-2.21/-0.51)</td>
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<tr>
<td></td>
<td>7.5 hours</td>
<td>-0.13 (-0.85/0.60)</td>
<td>0.775</td>
<td>-1.44 (-2.29/-0.58)</td>
</tr>
<tr>
<td></td>
<td>9 hours</td>
<td>0.42 (-0.30/1.14)</td>
<td>0.335</td>
<td>-1.10 (-1.95/-0.25)</td>
</tr>
<tr>
<td>Body sway</td>
<td>3 hours</td>
<td>1.46 (1.19/1.79)</td>
<td>0.002</td>
<td>0.99 (0.79/1.24)</td>
</tr>
<tr>
<td>(ratio)</td>
<td>4.5 hours</td>
<td>1.44 (1.18/1.77)</td>
<td>0.004</td>
<td>1.60 (1.30/1.95)</td>
</tr>
<tr>
<td></td>
<td>6 hours</td>
<td>1.42 (1.16/1.74)</td>
<td>0.005</td>
<td>1.58 (1.29/1.93)</td>
</tr>
<tr>
<td></td>
<td>7.5 hours</td>
<td>1.16 (0.95/1.42)</td>
<td>0.225</td>
<td>1.29 (1.05/1.58)</td>
</tr>
<tr>
<td></td>
<td>9 hours</td>
<td>1.00 (0.81/1.22)</td>
<td>0.977</td>
<td>1.16 (0.95/1.42)</td>
</tr>
<tr>
<td>Finger tapping</td>
<td>3 hours</td>
<td>-3.96 (-6.40/-1.52)</td>
<td>0.008</td>
<td>-0.30 (-2.64/2.04)</td>
</tr>
<tr>
<td>Adaptive</td>
<td>4.5 hours</td>
<td>-4.07 (-6.51/-1.63)</td>
<td>0.007</td>
<td>-3.37 (-5.47/-1.27)</td>
</tr>
<tr>
<td>tracking</td>
<td>6 hours</td>
<td>-5.63 (-8.07/-3.18)</td>
<td>&lt;0.001</td>
<td>-2.57 (-4.67/-0.47)</td>
</tr>
<tr>
<td></td>
<td>7.5 hours</td>
<td>-3.99 (-6.43/-1.55)</td>
<td>0.008</td>
<td>-2.35 (-4.45/-0.25)</td>
</tr>
<tr>
<td></td>
<td>9 hours</td>
<td>-3.26 (-5.70/-0.82)</td>
<td>0.029</td>
<td>-2.81 (-4.91/-0.72)</td>
</tr>
<tr>
<td>Adaptive</td>
<td>3 hours</td>
<td>0.18 (-2.84/3.19)</td>
<td>0.923</td>
<td>-2.90 (-6.66/0.86)</td>
</tr>
<tr>
<td>tracking</td>
<td>4.5 hours</td>
<td>-3.32 (-6.33/-0.31)</td>
<td>0.070</td>
<td>-8.20 (-11.56/-4.84)</td>
</tr>
<tr>
<td></td>
<td>6 hours</td>
<td>-3.64 (-6.72/-0.57)</td>
<td>0.052</td>
<td>-5.51 (-8.99/-2.03)</td>
</tr>
<tr>
<td></td>
<td>7.5 hours</td>
<td>-4.65 (-7.66/-1.64)</td>
<td>0.012</td>
<td>-4.50 (-7.86/-1.14)</td>
</tr>
<tr>
<td></td>
<td>9 hours</td>
<td>-0.52 (-3.58/2.54)</td>
<td>0.779</td>
<td>-1.88 (-5.24/1.48)</td>
</tr>
</tbody>
</table>

Results of psychomotor tests (n = 16) using change from baseline analysis. All results are expressed as differences in treatment means (with 90% confidence intervals and p-values), except body sway data which are expressed as geometric mean ratios (with 90% confidence intervals and p-values). Statistically significant results are indicated in bold.
Pharmacodynamics of Aprepitant

As demonstrated in Table 1, the CNS effects of aprepitant were limited. There was no impairment of DSST performance, VVLT performance, binary choice reaction time or any of the visual analogue scales, compared with placebo.

As demonstrated in Table 2, no clear effects on critical flicker fusion, body sway, finger tapping and adaptive tracking were demonstrated after administration of aprepitant compared to placebo.

Pharmacodynamics of Co-administration of Aprepitant and Alcohol

No statistically significant effects were observed in the results of DSST, binary choice reaction time or any of the visual analogue scales after co-administration of alcohol and aprepitant compared to administration of alcohol alone, as demonstrated in Table 1. Despite a longer reaction time (for incorrect answers) for immediate recognition after co-administration of alcohol and aprepitant compared to administration of alcohol alone ($p = 0.043$), no consistent effects of co-administration of aprepitant and alcohol on visual pattern recognition was observed.

As demonstrated in Table 2, no clear effects on critical flicker fusion, body sway, finger tapping and adaptive tracking were demonstrated after co-administration of alcohol and aprepitant compared with alcohol alone.

Discussion

This study had been performed primarily to evaluate central nervous system (CNS) effects of single oral doses of the now marketed NK$_1$ receptor antagonist aprepitant and possible interactions with alcohol in healthy volunteers, using an intravenous alcohol infusion paradigm to achieve pseudo-steady state levels of alcohol. Aprepitant was generally well tolerated in this study and adverse events were similar to those reported previously in healthy volunteers and patients with major depressive disorder, although diarrhea was not reported in our group of volunteers. Co-administration of aprepitant with intravenous alcohol infusion at pseudo-steady state was also generally well tolerated. Adverse events were comparable with those after administration of alcohol alone.

Following administration of aprepitant alone, no significant impairments were observed with either the cognitive or the psychomotor tests. This study represents the first use of this pharmacodynamic test battery to evaluate the effects of a selective NK$_1$ antagonist in healthy volunteers. As a result, no data of other selective NK$_1$ receptor antagonists are available for comparison with the effects of aprepitant. Recently, the NK$_3$ receptor antagonist talnetant has been
evaluated with this pharmacodynamic test battery in healthy volunteers. Single oral doses of 200 mg talnetant decreasedVAS calmness and alpha power EEG and improved adaptive tracking performance. However, differences in tissue expression of NK₁ and NK₃ receptors and differences in receptor affinity profiles of aprepitant and talnetant significantly limit the comparison of their effects. Another recent study using a similar pharmacodynamic test battery evaluated possible interactions of alcohol and GSK1144814, a dual antagonist at both NK₁ and NK₃ receptors. Co-administration of GSK1144814 and alcohol resulted in small additional impairments in saccadic reaction time and peak velocity, adaptive tracking performance, alertness, sleepiness, word recognition score and recognition reaction time at some point, compared with the effects of alcohol alone. The effects of GSK1144814 alone (without co-administration of alcohol) were not investigated, but the interaction with alcohol suggests that GSK1144814 either has small pharmacodynamic effects of its own or that GSK1144814 slightly modifies the effects of alcohol. However, the limited effect size of the interaction suggests that the pharmacodynamic effects of GSK1144814 are also limited. Therefore, antagonists at central NK₁ receptors seem to affect CNS performance of healthy volunteers to a rather limited extent.

Positron emission tomography (PET) using [¹⁸F]SPA-RQ in healthy volunteers has demonstrated that daily doses of 100 mg aprepitant or higher can achieve high levels (>90%) of NK₁ receptor occupancy in the striatum, which provides support for sufficient CNS penetration and NK₁ receptor occupancy by aprepitant at the dose employed in this study. Therefore, the limited effect size and scope of the CNS effects of aprepitant in this study do not seem to result from lack of central NK₁ receptor occupancy. It has been suggested that antagonism of neuropeptide receptors may show less dramatic effects than antagonism of classic neurotransmitter receptors, because the neuromodulatory nature of substance P and other neuropeptides seems to result in milder effects than drugs that interfere directly with the levels of monoamines and amino acid transmitters. In addition, much evidence indicates that neuropeptides are released after stressful and noxious stimuli. Accordingly, it has been suggested that neuropeptides exert their main action after various types of challenges or pathological conditions. Neuropeptide receptor antagonists might therefore have significant effects in pathological conditions with increased peptide release, whereas effects in normal healthy volunteers are limited.

In addition to obtaining a NK₁ receptor mediated profile of CNS effects, our study was specifically designed to evaluate potential interactions between aprepitant and alcohol. Pharmacokinetic interactions between aprepitant and alcohol were not expected, given their separate pathways of metabolism. Aprepi-
tant is metabolized primarily by CYP3A4\textsuperscript{10}, whereas alcohol is metabolized by a pathway that involves alcohol dehydrogenase, catalase and CYP2E\textsuperscript{11}, although alcohol has been suggested as a potential inducer of CYP3A4 activity\textsuperscript{39}. Plasma concentrations of aprepitant (see Figure 4) were statistically significantly higher when administered alone on day 9, compared with co-administration of alcohol on day 10, but the difference was quite small, with a cumulative mean difference in plasma concentrations of 11.3% (95% confidence interval: 3.9-18.2%), which might be considered not clinically meaningful. However, this study was not specifically designed to evaluate the induction of aprepitant metabolism by alcohol and there is a limitation with the statistical analysis, because treatments are sequential and not randomized.

Pharmacodynamic interactions between aprepitant and alcohol are theoretically possible as both compounds are centrally active and may influence several neurotransmitters, including dopamine, at various sites in the brain\textsuperscript{2,12}. The intravenous alcohol infusion produced clear and expected CNS effects, similar to previously reported results of this alcohol infusion paradigm\textsuperscript{13,19,20}. Contrary to those investigations, our study did not find a clear decrease in VAS alertness, but the visual analogue scales were performed shortly after the start of the alcohol infusion at which time blood alcohol concentration probably had not yet reached significant levels. Co-administration of aprepitant and alcohol did not result in significant additive effects, compared to the effects of alcohol alone, on any of the pharmacodynamic parameters, and is therefore not very likely to result in a clinically relevant interaction. To get a further impression of the effect size of pharmacodynamic effects, amitriptyline was included in this study as a pharmacodynamic comparator. Amitriptyline is one of the first ‘reference’ tricyclic antidepressant drugs\textsuperscript{40} and its CNS effects have long been known in the literature\textsuperscript{16}. Amitriptyline demonstrated significant and expected impairments in almost all pharmacodynamic parameters, in contrast with the limited effects of aprepitant. These findings generally confirmed the large functional CNS effects of a single dose of 50 mg amitriptyline, which were generally larger than those of alcohol levels above the legal driving limit in most Western countries.

In conclusion, our study demonstrates no significant CNS impairments after administration of aprepitant in healthy volunteers. Furthermore, co-administration of aprepitant with intravenous alcohol levels at pseudo-steady state was generally well tolerated and did not result in significant additive CNS effects, compared to the effects of alcohol alone. Therefore, our study found no indications for clinically relevant additive effects when alcohol is co-administered with aprepitant.
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3 Thorsell A, Schank JR, Singley E, Hunt SP, Heilig M (2010) Neurokinin-1 receptors (NK1R:S), alcohol consumption, and alcohol reward in mice. Psychopharmacology (Berl) 209: 103-111
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8 Seneviratne C, Ait-Daoud N, Ma JZ, Chen G, Johnson BA, Li MD (2009) Susceptibility locus in neurokinin-1 receptor gene associated with alcohol dependence. Neuropsychopharmacology 34: 2442-2449


