Pharmacokinetics and central nervous system effects of the novel dual NK₁/NK₃ receptor antagonist GSK1144814 in alcohol-intoxicated volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Antagonism of both NK₁ and NK₃ receptors may be an effective strategy in the pharmacotherapy of schizophrenia, drug addiction or depression. Alcohol is used frequently by patients with these conditions. GSK1144814 is a novel selective dual NK₁/NK₃ receptor antagonist in development.

WHAT THIS STUDY ADDS

- Administration of GSK1144814 in the presence of alcohol is generally well tolerated and does not notably affect alcohol pharmacokinetics. GSK1144814 does affect alcohol-induced impairment in several CNS parameters, but the differences are quite small and not very likely to produce clinically relevant additional impairments after alcohol consumption.

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AIMS

Antagonism of both NK₁ and NK₃ receptors may be an effective strategy in the pharmacotherapy of schizophrenia, drug addiction or depression. GSK1144814 is a novel selective dual NK₁/NK₃ receptor antagonist. The potential influence of GSK1144814 on the effects of alcohol was investigated.

METHODS

In a blinded, randomized, placebo-controlled, two period crossover study, the pharmacokinetics and central nervous system (CNS) effects of single oral doses of 200 mg GSK1144814 were evaluated in 20 healthy volunteers, using a controlled alcohol infusion paradigm to maintain stable alcohol concentrations with subsequent analysis of eye movements, adaptive tracking, body sway, visual analogue scales, Epworth sleepiness scale and the verbal visual learning test.

RESULTS

Frequent adverse effects were mild somnolence, fatigue and headache. Plasma concentration of GSK1144814 in the presence of alcohol was maximal 1.5 h after dose administration. GSK1144814 did not affect alcohol pharmacokinetics. Co-administration of GSK1144814 and alcohol impaired saccadic reaction time and peak velocity, adaptive tracking, alertness, sleepiness, word recognition and recognition reaction time compared with administration of alcohol alone, but the size of the interaction was small.

CONCLUSIONS

Administration of GSK1144814 in the presence of alcohol was generally well tolerated and not likely to produce clinically relevant additional impairments after alcohol consumption.

Introduction

Antagonists at the neurokinin-1 (NK₁) and neurokinin-3 (NK₃) receptors have been evaluated in several clinical trials for possible antidepressant and antipsychotic activity, respectively [1–3]. Clinical trials with the NK₁ receptor antagonists casopitant, aprepitant and L-759274 have demonstrated antidepressant efficacy [4–6], although these findings were not replicated for the latter two compounds [7, 8]. An early clinical trial with the NK₃ receptor antagonist osanetant has demonstrated antipsychotic efficacy in schizophrenic patients [9], but further clinical development of this compound has been discontinued because of poor pharmacokinetic characteristics [3, 10]. Development of another NK₃ receptor antagonist, talnetant, also has been discontinued, due to rather low penetration of the blood–brain barrier [3, 10]. Recently, interest in NK₁ and NK₃ receptor antagonists has focused on a potential role in the treatment of drug addiction and substance abuse disorders. Involvement of neurokinin receptors in the aetiology of substance abuse disorders has been suggested by recent studies, which identified haplotypes and single nucleotide polymorphisms (SNP) in the *NK1R* gene [11] and *TACR3* gene [12], encoding the NK₁ and NK₃ receptor respectively, that were significantly associated with the development of alcohol dependence. Pre-clinical studies in various animal models have demonstrated that pharmacological blockade of NK₁ receptors dose-dependently suppresses alcohol intake [13] and stress-induced re-instatement of alcohol seeking behaviour [14], while pharmacological blockade of NK₃ receptors attenuates the behavioural effects of cocaine [15, 16] and prevents behavioural sensitization to cocaine [17]. Furthermore, a recent clinical trial with the NK₁ receptor antagonist LY686017 in detoxified alcoholic inpatients has demonstrated suppression of spontaneous alcohol cravings and improved overall well-being [18]. Together, these data suggest that antagonism of both NK₁ and NK₃ receptors may be an effective strategy in pharmacotherapy of schizophrenia, drug addiction or depression, especially in patients with co-morbid schizophrenia and substance abuse disorder, which is quite common [19, 20] and is associated with poor clinical outcome [21, 22].

GSK1144814 is a novel selective high affinity ligand for recombinant human NK₁ and NK₃ receptors, that is being developed as a novel treatment for schizophrenia, depression and substance abuse disorders (data on file). Pre-clinical *in vitro* studies demonstrated that GSK1144814 was selective for the human NK₁ and NK₃ receptors, vs. 88 other non-tachykinin human receptors, enzymes and transporters (data on file). Previous studies of GSK1144814 in healthy volunteers demonstrated peak concentrations within 1 h and a terminal elimination half-life of roughly 15 h (data on file).

A potential role for GSK1144814 in the pharmacotherapy of drug abuse and addiction necessitates evalua-

tion of possible interactions with drugs of abuse, because the target population of patients will have alcohol dependence as a primary disorder or co-morbidity. Pharmacodynamic interactions are theoretically possible as both compounds are centrally active and may potentially influence several neurotransmitters, including dopamine, at various sites in the brain [23, 24]. NK₁ receptor antagonists with chemical structures similar to GSK1144814, such as casopitant [25] and aprepitant [26], are metabolized primarily by CYP3A4. In contrast, alcohol is metabolized by a pathway that involves alcohol dehydrogenase, catalase and CYP2E1 [27]. Accordingly, pharmacokinetic interactions between GSK1144814 and alcohol are not expected. Therefore, in the present study, we investigated whether single oral doses of GSK1144814 could modulate the central nervous system (CNS) effects of alcohol in healthy volunteers. An intravenous alcohol infusion paradigm [28] was used to achieve pseudo-steady-state alcohol concentrations, while either single oral doses of GSK1144814 or placebo were co-administered. A recent literature review [29] identified the most sensitive and useful functional biomarkers for the acute CNS effects of alcohol, which included divided attention, focused attention, visuomotor control, visual analogue scales for subjective effects, reaction time, working memory and inhibition, digit symbol substitution, motor control, postural stability and immediate recall (auditory or verbal memory). A previous study using the alcohol clamping method [30] demonstrated significant effects of alcohol on smooth pursuit eye movements, adaptive tracking, body sway and visual analogue scales for alertness and the subjective effects of alcohol, while the peak velocity of saccadic eye movements also seemed to decrease somewhat, albeit not statistically significantly. These quantitative tests were all included in the present study, while the visual verbal learning test (VVLTL) [31] was added to evaluate effects on memory. To our knowledge, no other NK₁/NK₃ receptor antagonists have been evaluated using these tests and we are unaware of other CNS tests capable of demonstrating effects in healthy volunteers after single oral doses. Thus, our study can be regarded as exploratory in that regard. However, the quantitative tests used in this study have previously been demonstrated to be sensitive to the central effects of various compounds, including antipsychotic drugs [32], antidepressant drugs [33] and the NK₃ receptor antagonist talnetant [34]. Finally, also for exploratory purposes, we included an adapted version of the Epworth sleepiness scale [35, 36] in this study to evaluate its usefulness for assessing drug-induced sleepiness in early phase clinical trials. An oral dose of 200 mg GSK1144814 was chosen based on observed pharmacokinetics in previous studies in healthy volunteers and on AUC and NOAEL estimations derived from animal models (data on file). This dose is generally well tolerated in healthy volunteers and can produce high levels of receptor occupancy (>99% NK₁ receptor occupancy in frontal cortex), as demonstrated by positron

emission tomography (PET) using [^{11}C]-GR205171 in healthy volunteers (data on file). To demonstrate that the effects of alcohol combined with GSK1144814 do not significantly differ from the effects of alcohol alone, we applied generally accepted statistical criteria for bioequivalence.

Methods

Study design

Twenty healthy volunteers, between 18 and 65 years of age and with a body mass index between 19 and 30 kg m⁻², were planned to participate in a blinded, randomized, placebo-controlled, two-period crossover study. The study was approved by the medical ethics review board of the Leiden University Medical Center and registered at the NIH database of clinical trials (website <http://clinicaltrials.gov>) with identifier NCT01181908 and GSK ID number 113476. Prior to medical screening, all volunteers gave written informed consent. Medical screening included a medical history, physical examination, urinalysis, routine haematology and chemistry, 12-lead electrocardiography (ECG) and 24 h Holter-ECG recording. All volunteers underwent training sessions for the pharmacodynamic tests in order to minimize possible learning effects.

Volunteers were assigned to a randomized treatment sequence, consisting of one study period of intravenous alcohol infusion (alcohol clamping, see below for further details) combined with oral administration of 200 mg GSK1144814 and one study period of intravenous alcohol infusion combined with oral placebo administration. GSK1144814 or matching placebo were administered orally 30 min after the start of the alcohol infusion. The alcohol infusion continued until 5 h after study drug administration, in order to coincide with the expected t_{max} of GSK1144814. Subjects remained in the clinic until 48 h after study drug administration. The first study period was preceded by a baseline study day in which all study-related activities were performed following unblinded intravenous saline infusion without drug administration, to familiarize all volunteers with the study-related procedures. All periods were separated by a wash-out time of approximately 7 days.

Subjects were excluded if they had an average weekly alcohol intake of greater than 14 units (in the case of females) or 21 units (in case of males). Subjects with a past history of alcohol abuse or dependence were excluded. Subjects were also excluded if they had a history of regular use of tobacco- or nicotine-containing products within 6 months prior to screening, as indicated by urinary cotinine concentrations. Subjects were instructed to abstain from alcoholic drinks on the day preceding all study periods and all subsequent study days. In addition, the use of tobacco products or illicit drugs was not permitted. In all study periods, breath alcohol measurements and urinary

cotinine analysis were performed to ascertain non-use of alcohol and tobacco. Also, urine drug screening for cocaine, amphetamine, methamphetamine, opiates (morphine), benzodiazepines, barbiturates, MDMA and THC (Innovacon, Inc., San Diego, California, USA) was performed to ascertain non-use of illicit drugs.

Alcohol clamping

The method for attaining constant alcohol concentrations has been described in detail elsewhere [28, 30]. In brief, alcohol (ethanol 10% w/v solution in 5% glucose) was infused intravenously over a period of 5.5 h in total, guided by breath alcohol measurements to achieve a pseudo-steady-state alcohol serum concentration of 0.6 g l⁻¹. This target concentration was chosen because it produces significant central nervous system effects without causing too many inadvertent effects and is considered safe, since it is only just above the legal driving limit in the Netherlands (i.e. 0.5 g l⁻¹). The alcohol infusion started 30 min prior to administration of GSK1144814. The infusion rate for the first 10 min was determined using individual demographic characteristics (weight, height, age and gender). Infusion rates were subsequently adjusted, guided by breath alcohol measurements at baseline and at every 5 min for the first 30 min after the start of the infusion, every 10 min for the next 30 min and then every 0.5 h until the end, using two calibrated Alco-Sensor IV Intoximeters (Honac, Apeldoorn, the Netherlands), which were alternated to avoid any fatigue of the apparatus. To prevent local pain at the beginning of the alcohol infusion, an additional diluting glucose 5% infusion at 100 ml h⁻¹ was administered to all participants during the first 10 min after the start of the alcohol infusion through the same infusion line. The time profiles of the individually adjusted infusion rates necessary to maintain a target alcohol serum concentration of 0.6 g l⁻¹ provided an indirect measure of individual alcohol pharmacokinetics and were subsequently used for statistical comparison between treatments.

Safety monitoring

Evaluation of adverse events, 12-lead electrocardiograms (ECG), blood pressure, heart rate, body temperature, urinalysis and blood sampling for haematology and chemistry were performed at regular time points after dose administration. Automated oscillometric blood pressures were measured using a Nihon-Kohden BSM-1101 K monitor or a Colin Pressmate BP 8800. ECGs were obtained with Cardiofax V equipped with ECAPS12 analysis program (Nihon-Kohden, Tokyo, Japan).

Pharmacokinetics

Venous blood samples for concentration analysis of GSK1144814 were collected prior to dose administration and at 30 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 h after dose administration. Plasma concentrations of

GSK1144814 were determined using protein precipitation followed by HPLC/MS/MS analysis with a lower limit of quantification (LLQ) of 1.5 ng ml⁻¹.

Pharmacodynamic testing

Pharmacodynamic measurements were performed as described previously [34, 37], prior to dose administration and at fixed time intervals at 1, 2, 3, 4.5 and 8 h after dose administration. Volunteers were tested individually in a quiet room with ambient illumination. Quantitative tests included measurements of smooth pursuit and saccadic eye movements, adaptive tracking, body sway, visual analogue scales and an adapted version of the Epworth sleepiness scale. In addition, the visual verbal learning test (VVL) was performed at 2 and 4.5 h after dose administration.

Analysis of eye movements

To evaluate oculomotor performance and sedation, smooth pursuit and saccadic eye movements were recorded as described previously [38–41], using a computer-based system for signal collection (Cambridge Electronic Design Ltd, Cambridge, UK) and amplification (Grass-Telefactor, An Astro-Med, Inc. Product Group, Braintree, USA), and disposable surface electrodes (Medicotest N-OO-S, Olstykke, Denmark). For smooth pursuit eye movements, a target light source moves sinusoidally over 20° eyeball rotation at frequencies ranging from 0.3 to 1.1 Hz. The time in which the eyes were in smooth pursuit was calculated for each frequency and expressed as the percentage of stimulus duration. The average percentage of smooth pursuit for all frequencies was used as the parameter. For saccadic eye movements, the target light source jumps from side to side. Peak velocity (° s⁻¹), reaction time and inaccuracy (%) were calculated for all artifact-free saccades.

Adaptive tracking

To evaluate visuo-motor coordination, the adaptive tracking task was performed as described previously [40–44], 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 3 min.

Body sway

Postural stability in the sagittal plane was measured with an apparatus similar to the Wright ataxiometer [45], using a string attached to the waist of the volunteer. Movements over a period of 2 min, while standing still with eyes closed, were integrated and expressed as mm sway.

Visual analogue scales

Subjective effects were quantified using a Dutch translation of the visual analogue scales (VAS), originally

described by Norris [46], to derive three composite factors corresponding to sedation, mood (contentedness) and calmness, as described by Bond & Lader [47]. In addition, a visual analogue scale was used to quantify the subjective effects of alcohol.

Epworth sleepiness scale

For exploratory purposes, an adapted version of the Epworth sleepiness scale [35, 36] was included in this study. The Epworth sleepiness scale is a self-administered scale for assessing subjective daytime sleepiness persisting from week to week, independent of changes with the time of day and from day to day. Eight specific situations are presented in a questionnaire and subjects are instructed to rate the chance they would have dozed when those situations occur in daily life in recent times, on a scale from 0 to 3 with increasing chance of dozing. Scores of individual items are summed to produce a total score. In this study, the volunteers were instructed to rate the chance of dozing in the recent hour instead of the recent days to weeks, to assess if the Epworth sleepiness scale is sensitive to single dose drug effects over the course of a few hours.

Visual verbal learning test

The VVL [31] is an adapted version of the auditory verbal learning test [48]. 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 min (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 and the number of correctly recognized words are analyzed.

Statistical analysis

Pharmacokinetic parameters of GSK1144814 in the presence of alcohol were determined based on the individual plasma concentration–time data, using WinNonlin professional edition software version 5.2 (Pharsight Corporation, Mountain View, California, USA) and included the maximum observed plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}) and area under the plasma concentration–time curve from time zero extrapolated to the last time of quantifiable concentration (AUC(0, t_{last}) and to 24 h post-dose (AUC(0, 24 h)).

Effects of GSK1144814 administration on the pharmacokinetics of alcohol were evaluated by comparing the rates of alcohol infusion necessary to maintain a pseudo-steady-state alcohol serum concentration of 0.6 g l⁻¹, using a mixed model analysis of variance with treatment, period, time and treatment by time as fixed factors and with subject, subject by treatment and subject by time as random factors.

Table 1

Summary of common adverse events, reported by two subjects or more. Incidence is based on the number of subjects, not the number of events

Adverse event	Alcohol infusion with placebo	Alcohol infusion with GSK1144814
Somnolence	7 (35%)	13 (65%)
Fatigue	6 (30%)	4 (20%)
Headache	5 (25%)	7 (35%)
Feeling drunk	6 (30%)	8 (40%)
Infusion reaction	3 (15%)	5 (25%)
Nausea	2 (10%)	3 (15%)
Phlebitis	1 (5%)	2 (10%)
Diarrhoea	0	2 (10%)
Dizziness	1 (5%)	2 (10%)
Light headedness	1 (5%)	2 (10%)
Vasovagal reaction	2 (10%)	1 (5%)

Pharmacodynamic parameters were compared using a mixed model analysis of variance with treatment, period, time and treatment by time as fixed factors and with subject and subject by period as random factors. Saccadic eye movement data (reaction time, peak velocity and inaccuracy) and body sway data were log-transformed prior to analysis. VVLT data were compared using a mixed model with treatment and period as fixed effects and subject as a random effect. Treatment differences with corresponding 90% confidence intervals were calculated. All calculations were performed using SAS for Windows version 9.1.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Subjects

Twenty healthy male volunteers were included in the study. Participants had a mean age of 27.6 years (range 18–62 years), weight of 75.9 kg (range 60–90 kg) and body mass index of 22.8 kg m⁻² (range 19.9–27.6 kg m⁻²). All volunteers completed both study periods and a follow-up visit, except one volunteer who completed both study periods but was subsequently lost to follow-up. Pharmacokinetic and pharmacodynamic data from this volunteer were included in the statistical analysis.

Clinical observations

All adverse events were transient and mild or moderate in severity and no serious adverse events occurred during the study. Overall, the most common adverse events were somnolence and fatigue (see Table 1). Somnolence, headache, infusion reaction (generally consisting of redness of skin and burning feeling at infusion site), nausea, phlebitis, diarrhoea, dizziness and light headedness were reported more frequently after co-administration of alcohol and GSK1144814, whereas fatigue and vasovagal reaction were

Figure 1

Breath alcohol concentrations after intravenous alcohol infusion starting at $t = -0.5$ h and continuing until $t = 5$ h, in combination with oral administration (at $t = 0$ h) of GSK1144814 (open circles) or placebo (closed circles). Means are presented with SDs as error bars. $\circ$, alcohol infusion + GSK1144814; $\bullet$, alcohol infusion + placebo

reported more frequently after administration of alcohol alone. There were no consistent and clinically relevant changes in vital signs, blood chemistry and haematology or any of the ECG intervals.

Pharmacokinetics

Following intravenous alcohol infusion, breath alcohol concentrations increased rapidly and remained constant at the target level all over the time of infusion (see Figure 1). The rate of alcohol infusion necessary to maintain a pseudo-steady-state alcohol serum concentration of 0.6 g l⁻¹ (see Figure 2) was not significantly different between administration of GSK1144814 and placebo capsules ($P = 0.5105$).

Following co-administration of 200 mg GSK1144814 and intravenous alcohol infusion, GSK1144814 was rapidly absorbed (see Figure 3). Median time to peak concentration (t_{max}) was 1.5 h (range 0.97–3.48 h). The geometric mean C_{max} was 1500 ng ml⁻¹ (coefficient of variation 21.6%, 95% confidence interval (CI) 1360, 1660). The geometric mean $AUC(0, t_{last})$ and $AUC(0, 24$ h) were 7680 ng ml⁻¹ h (coefficient of variation 29.7%, 95% CI 6700, 8800) and 7630 ng ml⁻¹ h (coefficient of variation 30.5%, 95% CI 6610, 8810), respectively.

Pharmacodynamics

Neurophysiological parameters are summarized in Table 2 and Figures 4, 5, 6 and 7. There was a statistically significant increase in saccadic reaction time at 1 h and a decrease in saccadic peak velocity at 4.5 h after co-administration of GSK1144814 and alcohol compared with administration of alcohol alone. A clear reduction of overall adaptive tracking performance was observed after co-administration of GSK1144814 and alcohol compared with alcohol alone,

Figure 2

Alcohol infusion rates necessary to maintain a pseudo-steady-state alcohol serum concentration of 0.6 g l^{-1} , starting at $t = -0.5 \text{ h}$ and continuing until $t = 5 \text{ h}$, in combination with oral administration (at $t = 0 \text{ h}$) of GSK1144814 (open circles) or placebo (closed circles). Means are presented with SDs as error bars. $\circ$, alcohol infusion + GSK1144814; $\bullet$, alcohol infusion + placebo

Figure 3

Plasma concentrations of GSK1144814 after oral administration at $t = 0 \text{ h}$, in combination with intravenous alcohol infusion starting at $t = -0.5 \text{ h}$ and continuing until $t = 5 \text{ h}$. Means are presented with SDs as error bars

although the time course of effects was not very consistent. Effects were statistically significant at 1, 4.5 and 8 h, while effects at 2 and 3 h were not statistically significant. There were no statistically significant differences in saccadic inaccuracy, smooth pursuit eye movements and body sway.

Subjective effects are summarized in Table 3 and Figures 8, 9 and 10. An increase in sedation was observed at 3 and 4.5 h after co-administration of GSK1144814 and alcohol compared with alcohol alone. There were no statistically significant differences in contentedness, calmness or the feeling of being drunk. The Epworth sleepiness scale

demonstrated a clear increase of sleepiness in the first 3 h after co-administration of GSK1144814 and alcohol compared with alcohol alone.

The results of the VLT are summarized in Table 4. There were no significant differences in immediate, delayed or relative recall, but word recognition score was reduced and recognition reaction time was increased after co-administration of GSK1144814 and alcohol compared with alcohol alone.

Discussion

A potential role of NK_1 and NK_3 antagonism in the treatment of substance abuse disorders and psychosis necessitates evaluation of possible pharmacokinetic and pharmacodynamic interaction with drugs of abuse. The present study was performed primarily to evaluate if single oral doses of GSK1144814 can modulate the CNS effects of alcohol in healthy volunteers, because the target population of patients will have alcohol dependence as a primary disorder or co-morbidity.

In general, administration of GSK1144814 in the presence of alcohol was well tolerated. Median time to peak concentration of GSK1144814 (t_{max}) in the presence of alcohol was 1.5 h while the mean C_{max} was 1500 ng ml^{-1} , which were in line with results from previous studies with GSK1144814 in healthy volunteers. Administration of GSK1144814 did not notably affect alcohol pharmacokinetics, as the infusion rates necessary to maintain stable alcohol concentrations were similar between treatment groups. However, administration of GSK1144814 did affect several alcohol-induced pharmacodynamic impairments. Saccadic reaction time, saccadic peak velocity and adaptive tracking performance, alertness, sleepiness, word recognition score and recognition reaction time were all impaired to a small extent at some point following co-administration of GSK1144814 and alcohol, compared with administration of alcohol alone. These interactions suggest either that GSK1144814 has mild pharmacodynamic effects of its own that are superimposed on those of alcohol or that GSK1144814 slightly modifies the effects of alcohol. However, the additional CNS effects were very limited in extent and are therefore not very likely to produce clinically relevant impairments on top of those of alcohol alone.

For exploratory purposes, we included an adapted version of the Epworth sleepiness scale in this study. The Epworth sleepiness scale [35, 36] was designed to measure only those components of daytime sleepiness that persist from week to week and longer in a given subject, independent of changes with the time of day and from day to day. However, by rating the subjective sleepiness in recent hours, instead of recent days to weeks, we used this scale to assess sleepiness over the course of a few hours following administration of GSK1144814. This adapted version of the

Table 2

Neurophysiological parameters. Treatment differences between co-administration of alcohol and GSK1144814 compared with co-administration of alcohol and placebo, are expressed as differences in treatment means (with 90% CIs and *P* values) or as geometric mean ratios (with 90% CIs and *P* values). Statistically significant results are indicated in bold. The alcohol infusion started 30 min prior to administration of GSK1144814 (at *t* = 0) and continued over a period of 5.5 h in total

Parameter	1 h post-dose	2 h post-dose	3 h post-dose	4.5 h post-dose	8 h post-dose	Overall
Saccadic peak velocity (deg s ⁻¹)						
Ratio	0.97	1.00	0.96	0.95	0.97	0.97
90% CI	0.93, 1.00	0.96, 1.04	0.92, 1.00	0.92, 0.99	0.94, 1.01	0.95, 0.99
<i>P</i> value	0.093	0.914	0.084	0.030	0.191	0.035
Saccadic inaccuracy (%)						
Ratio	1.04	1.13	1.10	1.10	1.04	1.08
90% CI	0.89, 1.21	1.00, 1.27	0.95, 1.26	0.95, 1.26	0.90, 1.20	1.01, 1.15
<i>P</i> value	0.663	0.104	0.277	0.269	0.652	0.058
Saccadic reaction time (s)						
Ratio	1.06	1.01	1.01	1.05	1.05	1.04
90% CI	1.02, 1.10	0.96, 1.06	0.97, 1.06	1.01, 1.09	1.00, 1.10	1.01, 1.07
<i>P</i> value	0.017	0.693	0.642	0.052	0.100	0.045
Smooth pursuit (%)						
Difference	2.04	-0.32	1.90	2.40	-1.83	0.84
90% CI	-0.75, 4.83	-2.76, 2.12	-0.51, 4.30	0.26, 4.54	-5.05, 1.39	-0.94, 2.62
<i>P</i> value	0.224	0.824	0.190	0.067	0.325	0.413
Adaptive tracking (%)						
Difference	-2.78	-1.63	-0.24	-2.02	-1.77	-1.69
90% CI	-4.24, -1.32	-3.41, 0.16	-1.73, 1.26	-3.42, -0.63	-2.97, -0.57	-2.65, -0.72
<i>P</i> value	0.004	0.132	0.788	0.022	0.019	0.007
Body sway (mm)						
Ratio	1.28	1.18	1.14	1.09	1.06	1.15
90% CI	0.99/1.64	0.96, 1.44	0.95, 1.36	0.95, 1.25	0.92, 1.23	1.00, 1.31
<i>P</i> value	0.107	0.187	0.235	0.278	0.466	0.097

Figure 4

Adaptive tracking performance after intravenous alcohol infusion combined with oral administration (at *t* = 0 h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents measurements following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —●—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

Figure 5

Body sway after intravenous alcohol infusion combined with oral administration (at *t* = 0 h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents measurements following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —●—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

Figure 6

Saccadic peak velocity after intravenous alcohol infusion combined with oral administration (at $t=0$ h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents measurements following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —●—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

Figure 7

Smooth pursuit measurements after intravenous alcohol infusion combined with oral administration (at $t=0$ h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents measurements following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —●—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

Epworth sleepiness scale clearly demonstrated an increased chance of sleepiness and was one of the most sensitive parameters for the effects of GSK1144814. These results indicate that the Epworth sleepiness scale may be a sensitive tool not only for long term assessment of drug-induced sleepiness, but also short term effects after a single dose.

In a recent alcohol interaction study (Te Beek *et al.* 2012, in preparation), the CNS effects of the NK₁ receptor

antagonist aprepitant were studied, with or without co-administration of alcohol, using pharmacodynamic tests similar to our present study. A therapeutic dose of 160 mg aprepitant did not significantly impair performance on the digit symbol substitution test (DSST), VVLT, binary choice reaction time, visual analogue scales, critical flicker fusion, body sway, finger tapping and adaptive tracking, nor were there any signs of a significant interaction with alcohol. In another recent study, the CNS effects of the NK₃ receptor antagonist talnetant were investigated, at a dose of 200 mg, which is at the low end of the range that is investigated in clinical trials [34]. Talnetant improved adaptive tracking performance, decreased α power electroencephalography (EEG), and reduced calmness, while VVLT performance, body sway, finger tapping, saccadic and smooth pursuit eye movements were not affected [34]. These studies suggest that single dose administration of NK₁ and NK₃ receptor antagonists affect CNS performance of healthy volunteers to a rather limited extent. The present study was not designed to examine the CNS effects of GSK1144814 alone. Therefore, it cannot be excluded that GSK1144814 by itself can cause limited CNS effects. It is theoretically conceivable that alcohol, which is an allosteric modulator of different transmembrane receptors, can change the properties of the ligand-receptor complex formed by GSK1144814 with its target receptors. However, the effects of GSK1144814 alone are unlikely to be large considering the limited extent of CNS effects observed with talnetant and aprepitant alone and the lack of significant interactions between alcohol and aprepitant. Moreover, in the present study, the addition of GSK1144814 to alcohol caused only a limited increase of a few CNS parameters, which also argues against large CNS effects of GSK1144814 by itself.

The relative lack of effects of NK₁ and NK₃ receptor antagonists in healthy volunteers seems to contrast with the rather widespread expression of NK₁ receptors [49–54] and NK₃ receptors [54, 55] in the human central nervous system, and with the many interactions of these targets with dopamine, serotonin, norepinephrine, acetylcholine and GABA [1, 3, 23]. 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 neuropeptides seems to result in milder effects than monoamines and amino acid transmitters and their direct agonists and antagonists [56]. In addition, much evidence indicates that neuropeptides are released after stressful and noxious stimuli [51, 56, 57]. Accordingly, it has been suggested that neuropeptides exert their main action after various types of challenges or pathological conditions [56, 57]. Neuropeptide receptor antagonists might therefore have significant effects in pathological conditions with increased peptide release, while effects in normal healthy volunteers are limited [56, 57]. However, it cannot be excluded that effects could have been detected more clearly after multi-

Table 3

Subjective effects. Treatment differences between co-administration of alcohol and GSK1144814 compared with co-administration of alcohol and placebo, are expressed as differences in treatment means (with 90% CIs and *P* values). Statistically significant results are indicated in bold. The alcohol infusion started 30 min prior to administration of GSK1144814 (at *t* = 0) and continued over a period of 5.5 h in total

Parameter	1 h post-dose	2 h post-dose	3 h post-dose	4.5 h post-dose	8 h post-dose	Overall
VAS sedation (mm)						
Difference	1.97	2.90	3.32	2.74	2.14	2.61
90% CI	−0.22, 4.16	−0.31, 6.11	0.91, 5.73	0.59, 4.89	−1.64, 5.92	0.82, 4.41
<i>P</i> value	0.134	0.133	0.028	0.041	0.343	0.022
VAS contentedness (mm)						
Difference	0.81	−0.19	−0.90	−0.15	1.64	0.24
90% CI	−1.31, 2.93	−2.86, 2.48	−2.56, 0.76	−1.79, 1.49	−0.25, 3.53	−1.30, 1.78
<i>P</i> value	0.517	0.903	0.355	0.876	0.151	0.783
VAS calmness (mm)						
Difference	−1.19	−0.95	−3.43	−0.15	0.73	−1.00
90% CI	−4.34, 1.97	−4.67, 2.77	−6.47, −0.38	−2.12, 1.82	−1.41, 2.86	−3.09, 1.09
<i>P</i> value	0.520	0.665	0.066	0.897	0.567	0.410
VAS alcohol effects (mm)						
Difference	1.24	2.55	3.30	5.30	0.50	2.58
90% CI	−7.73, 10.21	−8.50, 13.60	−5.56, 12.16	−2.00, 12.60	−1.61, 2.61	−4.00, 9.15
<i>P</i> value	0.816	0.698	0.532	0.227	0.688	0.509
Epworth sleepiness scale						
Difference	3.23	1.75	3.25	0.75	1.10	2.02
90% CI	1.53, 4.93	0.33, 3.17	1.61, 4.89	−0.64, 2.14	−1.25, 3.45	1.10, 2.93
<i>P</i> value	0.004	0.047	0.002	0.355	0.430	0.001

Figure 8

Visual analogue scale (VAS) sedation scores after intravenous alcohol infusion combined with oral administration (at *t* = 0 h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents scores following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —○—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

ple dosing with GSK1144814, after testing of other functional CNS domains, or after challenge tests of relevant functional or pharmacological systems.

In conclusion, our study demonstrated that administration of the novel dual NK₁/NK₃ receptor antagonist GSK1144814 in the presence of alcohol was generally well

Figure 9

Visual analogue scale (VAS) scores for the subjective effects of alcohol after intravenous alcohol infusion combined with oral administration (at *t* = 0 h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents scores following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —○—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

tolerated. Administration of GSK1144814 did not notably affect alcohol pharmacokinetics, but did affect alcohol-induced impairments in several CNS parameters. However, differences between the treatment groups were quite small and not very likely to produce clinically relevant additional impairments after alcohol consumption.

Figure 10

Epworth sleepiness scale scores after intravenous alcohol infusion combined with oral administration (at $t=0$ h) of either GSK1144814 (open circles) or placebo (closed circles). The grey curve represents scores following unblinded intravenous saline infusion (without drug administration) during a baseline study day preceding the first study period, which is included in the figure for reference. Means are presented with SDs as error bars. —●—, unblinded saline infusion; —○—, alcohol infusion + GSK1144814; —●—, alcohol infusion + placebo

Table 4

Results of the visual verbal learning test (VVL). Treatment differences between co-administration of alcohol and GSK1144814 compared with co-administration of alcohol and placebo, are expressed as differences in treatment means (with 90% CIs and P values). Statistically significant results are indicated in bold

Parameter	Difference (90% CI)	P value
Immediate recall 1 st trial (correct)	-0.20 (-1.24, 0.84)	0.742
Immediate recall 2 nd trial (correct)	-0.65 (-1.89, 0.59)	0.377
Immediate recall 3 rd trial (correct)	0.40 (-1.11, 1.91)	0.652
Delayed recall (correct)	-0.50 (-2.10, 1.10)	0.594
Relative recall (%)	-7.96 (-17.85, 1.93)	0.180
Word recognition (correct)	-2.33 (-4.19, -0.47)	0.043
Recognition time (correct)	68.44 (28.09, 108.80)	0.009

Competing Interests

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