CHAPTER 3

PSYCHOMOTOR AND COGNITIVE EFFECTS OF OF TALNETANT (SB223412) IN HEALTHY VOLUNTEERS COMPARED TO PLACEBO OR HALOPERIDOL

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Abstract

Central Nervous System (CNS) effects of talnetant, an NK-3 antagonist in development for schizophrenia, were compared to those of haloperidol and placebo. The study was randomised, double-blind, three-way crossover of talnetant 200 mg, haloperidol 3 mg or placebo. Twelve healthy males participated and EEG, saccadic and smooth pursuit eye movements, adaptive tracking, body sway, finger tapping, hormones, visual analogue scales (VAS) for alertness, mood and calmness and psychedelic effects, left/right distraction task, Tower of London and Visual and Verbal Learning Task were assessed. Haloperidol showed (difference to placebo; 95% CI; p-value) decreases in EEG α power (-0.87μV; -1.51/-0.22; p = 0.0110), saccadic inaccuracy (2.0%; 0.5/3.6; p = 0.0133), smooth pursuit eye movements (-7.5%; -12.0/-3.0; p = 0.0026), adaptive tracking (-3.5%; -5.4/-1.7; p = 0.0009), alertness (-6.8 mm; -11.1/-2.4; p = 0.0039), negative mood (-4.6 mm; -8.6/-0.6; p = 0.0266), the ability to control thoughts (1.2 mm; 0.2/2.3; p = 0.0214), and an increase of serum prolactin (ratio 4.1; 3.0/5.6; p < 0.0001). Talnetant showed decreased alpha power (-0.69 μV; -1.34/-0.04; p = 0.0390), improved adaptive tracking (1.9%; 0.1/3.7; p = 0.0370) and reduced calmness on VAS Bond and Lader (-4.5 mm; -8.0/-1.0; p = 0.0151). Haloperidol effects were predominantly CNS-depressant, while those of talnetant were slightly stimulatory.
The results suggest that talnetant penetrates the brain, but it remains to be established whether this dose is sufficient and whether the observed effect profile is class-specific for NK-3 antagonists.

Introduction

Although the atypical antipsychotic drugs are better tolerated than most of the older typical antipsychotics, these drugs still produce less than optimal improvements in quality of life, work and social function and can have serious side effects. It has become increasingly clear that the pathophysiology of schizophrenia probably results from more than dopaminergic dysfunction alone.
The neurokinins (NKs, also called tachykinins) are one of the largest families of peptides and play an important role in neurotransmission and neuromodulation in the central and peripheral nervous system (Tooney *et al*, 2000). The neurokinin receptor consists of three different receptor subtypes: NK1, NK2, and NK3. Recently, NK3 has become of interest with regard to schizophrenia (Spooren *et al*, 2005).

The mRNA encoding these receptors and NK3 agonist binding sites are consistently detected in areas clearly associated with those involved in psychosis and location for therapeutic effects of antipsychotic drugs (Harrison, 1999; Tooney *et al*, 2000; Langlois *et al*, 2001). Other animal studies suggest that NK3 receptors are located on the surface of dopamine cells within the major dopaminergic cell groups (Stoessl, 1994).

Activation of NK3 receptors leads to the release of the biogenic amines dopamine, serotonin, and norepinephrine. Antagonizing these receptors therefore reduces the excitatory activation (or hyperactivity) of some or all of these principal systems without affecting normal baseline activity. This includes a reduction in neurotransmitter release in their target regions, including dopamine in ventral and dorsal striatal regions. This would be expected to have a desirable effect on the positive symptoms of schizophrenia (Spooren *et al*, 2005). The question remains however whether these postulated mechanisms would make NK3-receptors a potential target for novel antipsychotic agents.

Additional support comes from a clinical trial in schizophrenia patients performed by Meltzer *et al* (Meltzer *et al*, 2004). The NK3 receptor antagonist osanetant showed consistent effects on positive symptoms

and Clinical Global Impression Severity of Illness (CGI-S) comparable to haloperidol, without having (worsening or improving) effects on negative or depressive symptoms. Strong effects on hallucinatory symptoms and an excellent tolerability profile were claimed. Side effects noted with osanetant did not differ from those observed with placebo treatment. Although the design of the study did not allow firm conclusions, osanetant showed evidence of efficacy in the treatment of schizophrenia and schizoaffective disorder.

Talnetant (SB223412) is a selective, competitive, non-peptide neurokinin-3 (NK3) receptor antagonist and is in development for the treatment of the positive symptoms of schizophrenia (Dawson L A *et al*, 2008). It was well tolerated in healthy volunteers, but the lack of clear central nervous system (CNS) effects in these early studies also precluded any conclusions about brain penetration and relevant pharmacological activity. The current study was therefore set up to determine the profile and time course of CNS-effects of talnetant 200 mg, and to compare these to the plasma concentrations. Haloperidol has found to be an effective agent in treatment of schizophrenia and has relative specificity for the dopamine2 post-synaptic receptor. Additionally haloperidol has clear CNS-effects in healthy volunteers (Beuzen *et al*, 1999; Legangneux *et al*, 2000; Pretorius *et al*, 2001). NK3 antagonists are hypothesised not to affect baseline dopamine activity, in contrast to haloperidol. Therefore, haloperidol was regarded as a good positive control. In this study the effects of a direct dopamine antagonist are compared to those of talnetant.

Methods and Materials

Subjects

Twelve healthy male and female volunteers aged 18-65 with BMI of 19-30kg/m3 were recruited by the Centre of Human Drug Research (CHDR). Exclusion criteria included the use of agents known to affect CNS performance (including smoking and drug or alcohol abuse) and evidence of relevant clinical abnormalities. The Ethics Review Board of the Leiden University Medical Center approved the study protocol. Written informed consent was obtained from all subjects following a written and oral explanation. The study was performed under Good Clinical Practice quality systems.

Study design

This was a placebo controlled, randomized, double-blind, three-way, cross-over, monocentric study in twelve healthy volunteers, with a two-week wash-out period. All subjects received single oral doses of talnetant 200mg, haloperidol 3mg or their matching double-dummy placebos. Administration sequence was determined using Latin squares balanced for first-order carry-over effects.

For the dosing sessions all participants were instructed to remain fasted from midnight. Smoking, the use of alcohol and quinine- or xanthine-containing foods or beverages was not allowed during the study days. After a standard breakfast at the Centre, patients received the study medication. A standardised lunch and dinner was offered at respectively 4 and 8 hours after drug intake. Water was allowed *ad libitum*. Subjects remained in house until 24 hours after the last study drug administration and returned to the clinic at 36 hours, 48, 72 hours and 7-14 days after dosing for a post-study follow up.

Pharmacokinetics

Blood samples were obtained predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours after dosing. Plasma samples were assayed for talnetant using a method based upon protein precipitation with acetonitrile followed by high performance chromatography/mass spectrometry (HPLC/MS/MS) employing positive-ion atmospheric pressure chemical ionization with a lower limit of quantification (LLQ) of 5.00 ng/mL for a 50mL aliquot of human plasma. For haloperidol the method was based upon solid phase extraction followed by LC/MS/MS analysis employing positive ion electrospray (ESI) ionization with LLQ of 0.0250 ng/mL for a 200mL aliquot of human plasma.

Pharmacokinetics (PK) of talnetant were determined using nonlinear mixed effect modelling as implemented in NONMEM Version V (GloboMax LLC, Hanover, MD, USA). A two-compartment model with first order absorption was used and parameters were estimated using first order conditional estimation on log-transformed data. This procedure implements the log-normal residual error model. Inter-individual variability in PK parameters was modelled using a constant CV (coefficient of variation) error model. The model was parameterised in terms of initial ($T_{1/2\alpha}$) and terminal half life ($T_{1/2\beta}$), absorption half life ($T_{1/2\alpha}$), central volume divided by bioavailability ($V_{C/F}$), the rate constant describing transfer from the peripheral to the central compartment (k_{32}), and absorption lag-time (t_{LAG}) (using NONMEM's Advan4 and Trans6).

Pharmacodynamics

All pharmacodynamic measurements were performed at -1, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours relative to drug intake. The pharmacodynamic assessments were obtained in a quiet room with subdued light with one subject per room using the 'Neurocart'. This is a transportable CNS measurement battery used for on-site assessment of drug effects and has been used in numerous studies with different kinds of CNS drugs at CHDR (de Haas *et al*, 2007; van Steveninck, 1993; van Steveninck *et al* 1996). It consists of a series of measurements that were chosen for their frequent repeatability, low variability, and their sensitivity to a wide range of drug-induced CNS-effects. Before the study, the subjects were familiarized with the test procedures during a training session, no more than one week before the start of the study.

ADAPTIVE TRACKING

Adaptive tracking measures visuo-motor coordination and vigilance (Borland and Nicholson, 1984) and was performed as originally described by Borland and Nicolson. The test was adapted for use on a personal computer. The adaptive tracking test is more sensitive to impairment of eye-hand coordination by drugs than compensatory pursuit tasks or other pursuit tracking tasks, such as the pursuit rotor.

The adaptive tracking test has proved to be useful for measurement of CNS effects of alcohol(van Steveninck), various psychoactive drugs (Borland and Nicholson, 1984; Cohen *et al*, 1985) and sleep deprivation (van Steveninck, 1993). The average performance over a 3-minute period was used for statistical analysis.

VISUAL AND VERBAL LEARNING TASK (VVLT)

Memory (impairment) is a difficult task to study due to the fact that there are so many different components of learning behaviour, i.e. acquisition, consolidation, storage and retrieval. Learning tasks often test only one of these components. However, the Visual Verbal Learning Test (VVLT) (Schmitt *et al*, 2000) contains three different subtests that cover most of the scope of learning behaviour, i.e. immediate and delayed word recall and a delayed word recognition (Schmitt *et al*, 2000). This test is an adapted version of the Auditory Verbal Learning Test (Rey). Thirty words are presented in the same sequence in three trials on a computer screen. Each trial ends with a free recall of the words (immediate recall). Thirty minutes after the first trial, the subject is requested to recall as many words as possible (delayed recall). This is followed by a recognition test, consisting of 15 previously presented words and 15 other but comparable words, in which the subject has to respond 'Yes/No' as quickly as possible to indicate recognition of the word (delayed recognition).

At CHDR this test has shown the CNS effects of various compounds such as benzodiazepines (de Haas *et al*, 2007), cannabis, scopolamine, and risperidone [CHDR data on file]. Outcome variables for the immediate and delayed word recall were the average and the maximum number of correct responses. For the delayed word recognition, the number of correct items and mean response time for correct responses were analysed.

TOWER OF LONDON

Planning capacity can be assessed by a modified version of the One-touch Tower of London (TOL) task (Sobczak *et al*, 2002). This test showed effects for several different CNS active drugs (Beuzen *et al*, 1999; Sobczak *et al* 2002). The test consists of three coloured balls which must be arranged on three sticks to match a picture with the goal positions. The complexity of

the problem is altered by varying the minimum number of moves to reach the goal positions. Each trial consisted of a two- to seven move problem. Prior to each problem, the subjects are informed about the minimum number of moves in which the problem can be solved. Performance was indicated by the slope coefficient of the linear regression of the median response time as a function of the number of steps.

BODY SWAY

An apparatus similar to Wright's ataxiameter was used to measure postural stability, by integrating the amplitude of body movement, transferred through a string attached to the subject's waist (TNO/NIPG, Leiden, The Netherlands) (Wright, 1971). Two-minute measurements were made in the antero-posterior direction with the eyes closed, standing with feet slightly apart wearing comfortable low-heeled shoes. The total amount of movement (in centimeters over 2 min) was used for statistical analysis.

LEFT/RIGHT DISTRACTION TASK

A parametric version of the well-known colour-word response conflict task (Stroop, 1935) was used to measure inhibition by an intervention (Laeng *et al*, 2005). In the past it has been used to measure the effects of several compounds including antipsychotics (Cuesta *et al*, 2001). The words Left and Right are displayed either at the left or the right side of a computer screen. Response instructions were to respond quickly (by pressing a corresponding button) to the location of the word irrespective of its meaning. The output parameters are the response time and accuracy of responding as a function of task difficulty.

FINGER TAPPING

The finger tapping test evaluates motor activation and fluency and was adapted from the Halstead Reitan Test Battery (Yeudall *et al*, 1987). The test Speed of finger tapping was measured for the index finger of the dominant hand; a session contained five performances of ten seconds. The volunteer was instructed to tap as quickly as possible on the space bar of a computer. The mean tapping rate and the standard deviations are used for statistical analysis.

ELECTROENCEPHALOGRAPHY (EEG)

EEG was measured to provide measures of CNS functions (Cohen *et al*1985). In addition, the literature suggests that antipsychotics show distinct profiles of EEG-changes (de Visser *et al*, 2001; Saletu *et al*, 1987). EEG recordings were made using disposable silver-silver chloride electrodes (Medicotest N-00-S, Olstykke, Denmark), fixed with collodion at Fz, Cz, Pz and Oz (international 10/20 system). The electrode resistances were kept below 5 kOhm and EEG signals obtained from leads Fz-Cz and Pz-Oz. The signals were amplified by use of Nihon Kohden AB-621G bioelectric amplifier (Nihon Kohden Corporation, Tokyo, Japan) with a time constant of 0.3 seconds and a low pass filter at 100 Hz. For the fast Fourier analysis, data collection and analysis were performed using customised CED software (Cambridge Electronics Design, Cambridge, UK) and stored on hard disk for subsequent analysis. Data blocks containing artefacts were identified by visual inspection and these were excluded from analysis. Fast Fourier transform analysis was performed to obtain the absolute power in the delta- (0.5-3.5 Hz), theta- (3.5-7.5 Hz), alpha- (7.5-11.5 Hz) and beta- (11.5-30 Hz) frequency ranges. The duration of EEG measurements was 2 minutes per session and eyes were closed.

EYE MOVEMENT ANALYSIS

Saccadic and smooth pursuit eye movements were recorded as described previously (van Steveninck *et al*, 1996; van Steveninck, 1993) and have shown effects on many different CNS active drugs, including GABA-ergic (de Visser *et al* 2001; de Haas *et al*, 2007), serotonergic (Gijsman *et al*, 2002), noradrenergic (de Visser *et al*, 2001; van der Post *et al* 2004; Kemme *et al*, 2003), and dopaminergic drugs (de Visser *et al*, 2001). The following equipment was used: a micro-computer based system for data recording and analysis (Cambridge Electronics Design, Cambridge, UK), Nihon Kohden equipment for stimulus display, signal collection and amplification (Nihon Kohden Corporation, Tokyo, Japan) and disposable

surface electrodes (Medicotest N-00-S, Olstykke, Denmark). Average values of latency (= reaction time), peak saccadic velocity and inaccuracy of all artefact-free saccades were used as parameters for saccadic eye movements. Saccadic inaccuracy was calculated as the absolute value of the difference between the stimulus angle and the corresponding saccade, expressed as a percentage of the stimulus angle. The higher the percentage, the worse the performance of the eye movement test. For smooth pursuit, the target moved sinusoidally over 20 degrees of eyeball rotation, at frequencies ranging from 0.3-1.1 Hz. The main parameter was the percentage of time that the eyes were in smooth pursuit of the target.

CORTISOL AND PROLACTIN (PRL)

It is well known that antipsychotics can cause prolactin increase which can lead to clinically undesirable effects(de Visser *et al*, 2001). Blood samples were collected in plain 3mL tubes in order to assess serum levels of cortisol and prolactin (PRL). Serum was separated by refrigerated centrifugation (2000 g at 4°C for ten minutes) within one hour of collection, and transferred to appropriately labelled polypropylene tubes. Serum specimens were stored at -20°C until analysis.

VISUAL ANALOGUE SCALES (VAS)

Visual analogue scales consist of 100 millimeter line segments. Subjects put a mark on a point on the line that best represents their subjective state corresponding to the condition tested. The result is a distance (millimeters) calculated from the mark on the line.

These measures have been shown effects on many different CNS active drugs, including sedative agents (van Steveninck *et al*, 1996; de Haas *et al*, 2007; Norris, 1971), and dopaminergic drugs (de Visser *et al*, 2001).

Subjective effects were quantified using a Dutch translation of the 16 visual analogue scales (VAS) originally described by Norris (Norris, 1971) and applied to drug effect by Bond and Lader. From the set of 16 scales, three factors corresponding to alertness (from nine scores), mood (or contentedness; from five scores), and calmness (from two scores) were derived (Bond and Lader, 1994). A lower score on these scales indicate sedation, excitation and decrease in mood (or contentedness) respectively.

In addition, 13 VAS described by Bowdle (Bowdle *et al*, 1998) assessed the psychedelic effects of the drug. The lowest extreme is usually '0', signifying complete absence of the state (which will be the case under normal circumstances). The highest end of the scale is equivalent with the 'most extreme state imaginable'.

Statistical analysis

All PD endpoints were analysed separately by mixed model analyses of variance (using SAS PROC MIXED) with subject subject-by-treatment and subject-by-time as random effect and treatment, occasion (= period), time and treatment by time as fixed effects, where the baseline value was included as covariate. Graphs of the Least Squares Means estimates over time by treatment were presented with 95% confidence intervals as error bars. Calculation of time and treatment by time effects was for graphical presentation purposes only. Treatment effect was reported as the contrast between placebo and either haloperidol or talnetant where the average of the measurements up to (and including) 10 hours was calculated within the statistical model. All calculations were performed using SAS software (V8.2, SAS Institute, Inc., Cary, NC, USA).

Results

Participant characteristics

Eight males and five females were included in the study. One participant was withdrawn after the first dosing session (talnetant) due to a protocol deviation (undisclosed psychiatric history). Twelve subjects completed the study. Mean (SD) age, height, weight, and body mass index (BMI) of the subjects were 24 (4.6), 178 (7.3), 74.3 (9.1), and 23.6 (3.19) respectively.

Pharmacodynamic results

Since haloperidol was used as a reference dopaminergic agent, the effects of this positive control will be presented before the results of talnetant.

HALOPERIDOL EFFECTS

Haloperidol at a single dose of 3mg was generally well tolerated, with no more than mild adverse events in most subjects. There were no withdrawals due to adverse events and no serious or severe adverse events. Nonetheless, we found a considerable number of effects on neurophysiology and performance. Six subjects reported somnolence and five fatigue. In the results section, differences between treatments were defined as a statistically significant effect at a p-value of 0.05 or lower, without corrections for the number of assessments. The corresponding confidence intervals are shown in the tables 1-4. Haloperidol 3mg caused decreases in alpha power for the summed leads of Pz-Oz and Fz-Cz (table 1). Only absolute power was reported, but similar results were found for total and relative power (data not shown). Haloperidol effects started at one hour after dosing (figure 1).

Haloperidol increased saccadic inaccuracy compared to placebo (table 2). Haloperidol also affected smooth pursuit eye movements. Compared to placebo, treatment with haloperidol caused poorer performance and a clear steady decrease in smooth pursuit eye movements after haloperidol administration was seen.

Adaptive tracking performance deteriorated after haloperidol (difference of -3.5%; 95% CI, -5.4, -1.7%; not shown in table). The time-course of the effects (see figure 2) showed a clear and consistent reduction in tracking performance in the 4-10 hour observation period.

Haloperidol reduced alertness and mood (or contentedness) as indicated by the visual analogue scales (VAS) according to Bond and Lader (table 3). The time-profiles for VAS-alertness and mood showed transient decreases around 4-6 hours after dosing.

Haloperidol affected the VAS of psychedelic effects on item five ('it was difficult to control my thoughts') in comparison to placebo (table 3). The effects mainly occurred six hours post-dose.

Haloperidol caused impairment in the number of correct items after delayed recall (table 4).

Haloperidol caused a prolactin elevation (figure 3), with an increased C_{MAX} (ratio of 4.1; 95% CI, 3.0, 5.6) and a higher Area Under the Curve (AUC) up to 10hr (ratio of 3.1; 95% CI, 2.5, 3.8). Later time-points were not analysed. The time-course showed a clear drug effect from 3-12 hours after dosing, with a maximum around 5-6 hours (figure 3).

Haloperidol did not affect any other PD measures.

TALNETANT EFFECTS

Talnetant was tolerated very well at a dose of 200mg, and it was comparable to placebo in its adverse effects profile. Talnetant was associated with a similar amount of somnolence reports (i.e. three) and headache (i.e. one) as placebo. No other adverse effects were reported for talnetant. There were no withdrawals due to adverse events and no serious or severe adverse events.

The alpha power decreased for talnetant (table 1). The time-course in figure 1 (right panel) showed a decrease for six hours after dosing, which remained detectable for the rest of the ten-hour observation period. Talnetant improved adaptive tracking performance compared to placebo (difference of 1.9%; 95% CI, 0.1, 3.7%; not shown in table). The time-course of the effects suggested a slow increase up to four hours, after which the performance stabilised for the remainder of the observation period (figure 2).

Talnetant reduced feelings of calmness, as indicated by lower scores on the visual analogue scales (VAS) according to Bond and Lader (table 3).

Talnetant did not affect any other PD measures. The data did not allow an analysis of quantitative pharmacokinetic/pharmacodynamic relationships. However, the average time-courses of the effects of talnetant were in agreement with the concentration profile of the compound.

Most effects of talnetant differed from those of haloperidol, both in extent and character (table 6). It was associated with fewer reports of somnolence (i.e. three versus six) and fatigue (no reports versus five) than haloperidol. The alpha power decreased for talnetant and haloperidol to a comparable extent.

Contrary to what was observed for haloperidol, talnetant did not affect saccadic inaccuracy or smooth pursuit eye movements. Also in contrast with haloperidol, talnetant improved adaptive tracking performance compared to placebo. Talnetant reduced calmness of the visual analogue scales (VAS) according to Bond and Lader, for which no change was seen after haloperidol. Contrary to the effects seen with haloperidol, talnetant had no subjective effects on alertness or mood, nor on 'difficulty controlling thoughts' or any of the other Bowdle VAS-scores. Talnetant also did not affect memory, which showed impairments in delayed recall with haloperidol. There were no talnetant effects on serum prolactin level, which also differed from the increase seen with haloperidol.

Pharmacokinetic results

Plasma data are portrayed in figure 4 and NONMEM PK parameters estimates in table 5. The haloperidol plasma profile was similar to that of talnetant, showing a long elimination time with peak plasma concentrations of about 1ng/mL at around 5h and a terminal half life of approximately 30h.

Discussion

This study was performed to evaluate the effects of talnetant, a potential NK3 receptor antagonist, on a battery of quantitative CNS-tests in healthy volunteers, prior to studying its effects in patients. These tests were chosen for their sensitivity to classic neuroleptic agents and other CNS-active drugs (de Visser *et al*, 2001). Haloperidol was chosen as a positive control to prove the sensitivity of the test battery as it was tested before using similar tests (Beuzen *et al*, 1999; Legangneux *et al*, 2000; Pretorius *et al*, 2001). As haloperidol is a relatively selective D_2 antagonist, comparison of the effects of talnetant and haloperidol might give an indication how talnetant would affect the dopaminergic system in healthy subjects.

For this study, a 3 mg dose of haloperidol was selected. While the therapeutic dose range for psychosis in patients is 4 to 10 mg per day, King (King, 1997) recommended a maximum dose of haloperidol 3 mg for healthy volunteer studies. In doses of 1 or 2 mg it is not reliably distinguished from placebo(King ,1997; Legangneux *et al*, 2000). Above 3 mg, there is a dose-dependent rise in reported adverse effects reaching 80 percent at 6 mg (King, 1994).

From this study it was apparent that the pharmacological effects of the two compounds (in the used doses) differ. Haloperidol caused more (predictable) adverse effects than talnetant or placebo. In addition, there were also several differences in the CNS-effect profile. The only comparable effects of haloperidol and talnetant were on EEG alpha power. A reduction in alpha power is shown by many CNS-active drugs, particularly but not exclusively by sedative compounds, and it is not specific for dopaminergic activity (Chavanon *et al*, 2007). Other than this, talnetant effects differed from those of haloperidol. The combination of improved adaptive tracking and reduced calmness could be an indication for slight stimulation. However, these conclusions should be critically evaluated.

First, the talnetant effects were small and it could be argued that these were spurious. The study included many endpoints, and there was no correction for multiple comparisons. The increase in adaptive tracking and decrease in alpha power were marginally significant. Additionally, as the calmness VAS is an individual item of the VAS Bond & Lader, it can be questioned whether this subscale is sufficiently reliable. However, in our experience false-positive statistically significant results are quite rare with this study design, which uses conservative statistical methods based on overall average response, and robust CNS-function tests. So far, we have never observed unexpected statistical significance for stimulatory effects.

The reliability of the design is also confirmed by the effects of haloperidol, which were consistent with earlier reported studies in healthy volunteers (Legangneux *et al*, 2000; Pretorius *et al*, 2001) and with the expected effects of haloperidol in clinical studies (McCue *et al*, 2006).

Second, in the current study the mild stimulant effects of talnetant were only examined at a single dose of 200mg. The effects of higher doses cannot be predicted from these findings. The reason is that some drugs show a dose-related CNS-excitation. For example Selective Serotonin Reuptake Inhibitors (Dumont *et al*, 2005) are mildly stimulatory at low doses, and slightly depressant at higher levels. This study has identified several measurements that can be studied across a wider dose range to investigate the dose-response relationships. Unfortunately, the identification of clear drug-response patterns for talnetant (i.e. a pharmacokinetic-pharmacodynamic (PK/PD) relationship) was precluded by the small effect size and the protracted concentration profile. This was partly due to talnetant's relatively long T_{MAX} and $T_{1/2}$, and the relatively short evaluation period of CNS-effects.

Third, it is still unknown how the effects found in healthy volunteers can be extrapolated to patients. Studies in patients are needed to determine whether talnetant will have the desired effect in schizophrenia and whether the therapeutic window will be improved in comparison with the currently used antipsychotics. The only clinical data available to date demonstrated that osanetant, also an NK3 receptor antagonist, showed antipsychotic activity without any sedative adverse effects(Meltzer *et al*, 2004). The side effect profile of talnetant observed in this study seems consistent with the lack of adverse effects reported for osanetant. Although the effective therapeutic dose is still unknown, the short-term CNS pharmacodynamic effects of talnetant 200 mg in this study, which may provide indications for acute dose-related clinical events in patients, favour talnetant over haloperidol. Most adverse events on these treatments were mild and thought to be unrelated to treatment. Adaptive tracking is a measure of visuo-motor coordination and vigilance and smooth eye pursuit of visual coordination and attention. These parameters show basically opposing effects of haloperidol and talnetant, suggesting that talnetant might not exhibit the typical adverse events of antipsychotic drugs. Possibly, talnetant may be slightly stimulant, but the clinical consequences of this property remain to be established. As expected, haloperidol also showed clear effects on serum prolactin. Talnetant did not cause any hormonal changes, suggesting that this drug might not induce hyperprolactinaemia and its associated problems in patients.

Summarising, it remains to be seen if the identified effects of talnetant are either dose-dependent or class-specific for NK_3 antagonists. The results suggest that talnetant 200 mg will not exhibit the (side) effect profile of antipsychotics, but the clinical relevance of these effects and the therapeutic dose still need to be established. Clearly, other studies with different NK_3 antagonists, are needed to confirm that this drug class may cause slight CNS-stimulation in healthy subjects.

Table 1 Pharmacodynamic EEG effects of haloperidol and talnetant versus placebo

Parameter	Placebo	Haloperidol			Talnetant		
	LS mean[A] placebo	LS mean[A] haloperidol	Difference haloperidol - placebo	95% CI haloperidol - placebo[B]	LS mean[A] talnetant	Difference talnetant - placebo	95% CI talnetant - placebo[B]
Alpha-power summed leads (μV)	8.27	7.40	-0.87	-1.51, -0.22	7.58	-0.69	-1.34, -0.04
Beta-power summed leads (μV)	3.45	3.54	0.09	-0.16, 0.34	3.57	0.13	-0.13, 0.38
Delta-power summed leads (μV)	8.24	8.44	0.20	-0.67, 1.08	8.04	-0.20	-1.09, 0.69
Theta-power summed leads (μV)	5.58	5.62	0.05	-0.32, 0.41	5.70	0.12	-0.25, 0.49

A. LS mean is the Least Squares Means estimate; B. If 0 is included in the 95% Confidence Interval (95% CI) the difference is not conventionally different at the 5% level

Table 2 Pharmacodynamic eye movement effects of haloperidol and talnetant versus placebo

Parameter	Placebo	Haloperidol			Talnetant		
	LS mean[A] placebo	LS mean[A] haloperidol	Difference haloperidol - placebo	95% CI haloperidol - placebo[B]	LS mean[A] talnetant	Difference talnetant - placebo	95% CI talnetant - placebo[B]
Saccadic Peak Velocity (deg/sec)	471.3	467.1	-4.2	-21.4, 12.9	475.8	4.5	-12.8, 21.7
Saccadic Latency (sec)	0.204	0.213	0.009	-0.003, 0.021	0.204	-0.000	-0.012, 0.012
Saccadic Inaccuracy (%)	5.6	7.6	2.0	0.5, 3.6	6.3	0.7	-0.8, 2.3
Smooth pursuit (%)	57.9	50.4	-7.5	-12.0, -3.0	58.5	0.6	-4.0, 5.1

A. LS mean is the Least Squares Means estimate; B. If 0 is included in the 95% Confidence Interval (95% CI) the difference is not conventionally different at the 5% level

Table 3 Pharmacodynamic VAS effects of haloperidol and talnetant versus placebo

Parameter	Placebo	Haloperidol			Talnetant		
	LS mean[A] placebo	LS mean[A] haloperidol	Difference haloperidol-placebo	95% CI haloperidol-placebo[B]	LS mean[A] talnetant	Difference talnetant - placebo	95% CI talnetant - placebo[B]
VAS Alertness Bond and Lader (mm)	81.1	74.3	-6.8	-11.1, -2.4	80.1	-1.0	-5.2, 3.2
VAS Calmness Bond and Lader (mm)	90.8	88.8	-2.1	-5.6, 1.4	86.3	-4.5	-8.0, -1.0
VAS Mood Bond and Lader (mm)	89.5	84.9	-4.6	-8.6, -0.6	87.3	-2.2	-6.2, 1.7
Psychedelic VAS score 5 (mm)	0.4	1.7	1.2	0.2, 2.3	0.9	0.5	-0.5, 1.5

A. LS mean is the Least Squares Means estimate; B. If 0 is included in the 95% Confidence Interval (95% CI) the difference is not conventionally different at the 5% level

Table 4 Pharmacodynamic word recall effects of haloperidol and talnetant versus placebo

Parameter	Placebo	Haloperidol			Talnetant		
	LS mean[A] placebo	LS mean[A] haloperidol	Difference haloperidol-placebo	95% CI haloperidol-placebo[B]	LS mean[A] talnetant	Difference talnetant - placebo	95% CI talnetant - placebo[B]
Immediate word recall number correct -trial 3	17.75	16.08	-1.67	-4.27, 0.94	17.00	-0.75	-3.36, 1.86
Delayed word recall number correct	13.33	10.42	-2.92	-5.30, -0.54	13.50	0.17	-2.21, 2.55
Delayed word recognition number correct	22.50	24.00	1.50	-1.52, 4.52	24.58	2.08	-0.93, 5.10
Delayed word recognition average reaction time correct (msec)	945.36	900.54	-44.82	-148.6, 58.93	878.23	-67.13	-170.9, 36.61

A. LS mean is the Least Squares Means estimate; B. If 0 is included in the 95% Confidence Interval (95% CI) the difference is not conventionally different at the 5% level

Table 5 Pharmacokinetic Parameter estimates for talnetant (n = 13)

	Mean[A]	SEM[B]	CV[C]
$T_{1/2\alpha}$ (hr)	2.56	1.20	15.7%
$T_{1/2\beta}$ (hr)	42.1	5.15	34.9%
$t_{1/2A}$ (hr)	1.17	0.504	29.0%
V_C/F (L)	22.8	7.56	18.7%
K_{32} (hr^{-1})	0.105	0.0224	3.9%
t_{LAG} (hr)	0.704	0.118	28.1%
CL (L/hr)[D]	0.957	0.0976	36.1%

A. population average; B. standard error of the population average; C. inter-individual coefficient of variation - residual error (CV) = 10.2%; D. obtained from an alternative parameterization

Table 6 Overview of haloperidol and talnetant effects compared to placebo on different pharmacodynamic tests [A]

Pharmacodynamic test	Haloperidol	Talnetant
Alpha-power summed leads	-	-
Beta/Delta/Theta-power summed leads	0	0
Saccadic Peak Velocity and Latency	0	0
Saccadic Inaccuracy	+	0
Smooth pursuit	--	0
Average adaptive tracking	---	+
VAS Alertness Bond and Lader	--	0
VAS Calmness Bond and Lader	0	-
VAS Mood Bond and Lader	-	0
Psychedelic VAS score 5	+	0
Immediate word recall number correct -trial 3	0	0
Delayed word recall number correct	-	0
Delayed word recognition number correct and average reaction time correct	0	0
AUC up to 10hr and C_{MAX} cortisol serum level	0	0
AUC up to 10hr and C_{MAX} prolactin serum level	++++	0

A. classified as follows: '0' indicates no statistically significant decrease or increase; '-' or '+' indicates a decrease or increase showing a p-value less than 0.05; '--' or '++' indicates a decrease or increase showing a p-value less than 0.01; '---' or '+++' indicates a decrease or increase showing a p-value less than 0.001; '----' or '++++' indicates a decrease or increase showing a p-value less than 0.0001

Figure 1 Adjusted (for baseline) mean time profile of EEG α-power summed leads with 95% CI for placebo and lower 95%CI for talnetant (circle, talnetant; square, haloperidol; dot, placebo).

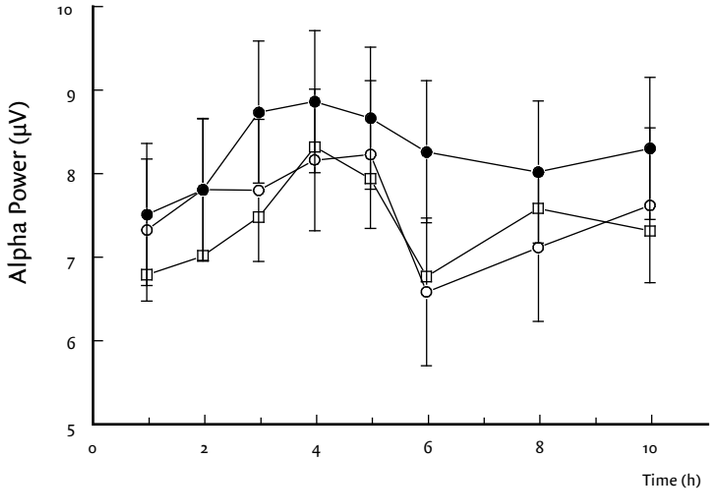


Figure 2 Adjusted (for baseline) mean time profile of average performance on adaptive tracking with 95% CI for talnetant and lower 95% CI for haloperidol (circle, talnetant; square, haloperidol; dot, placebo).

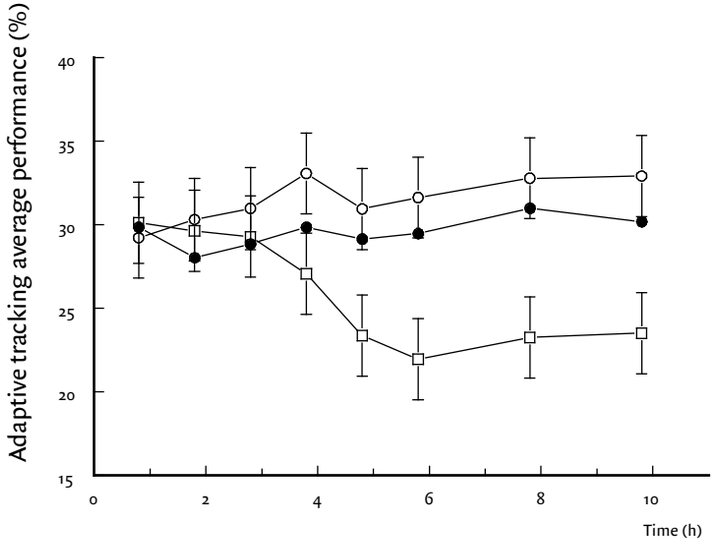


Figure 3 Average (+SD) serum concentration profile of prolactin (circle: talnetant; square: haloperidol; dot: placebo)

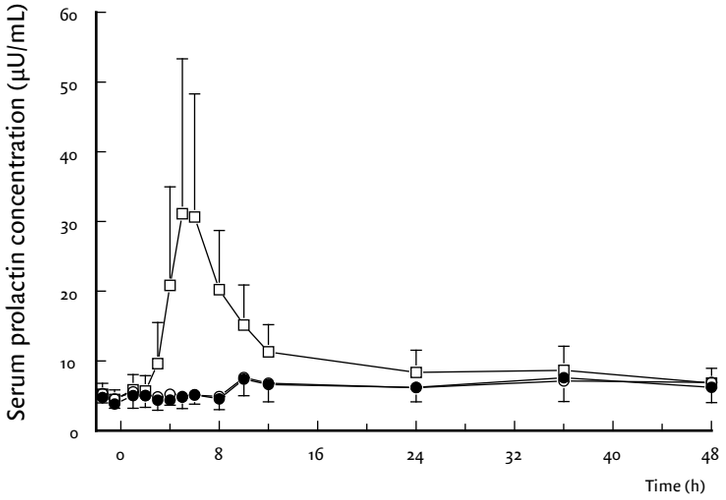
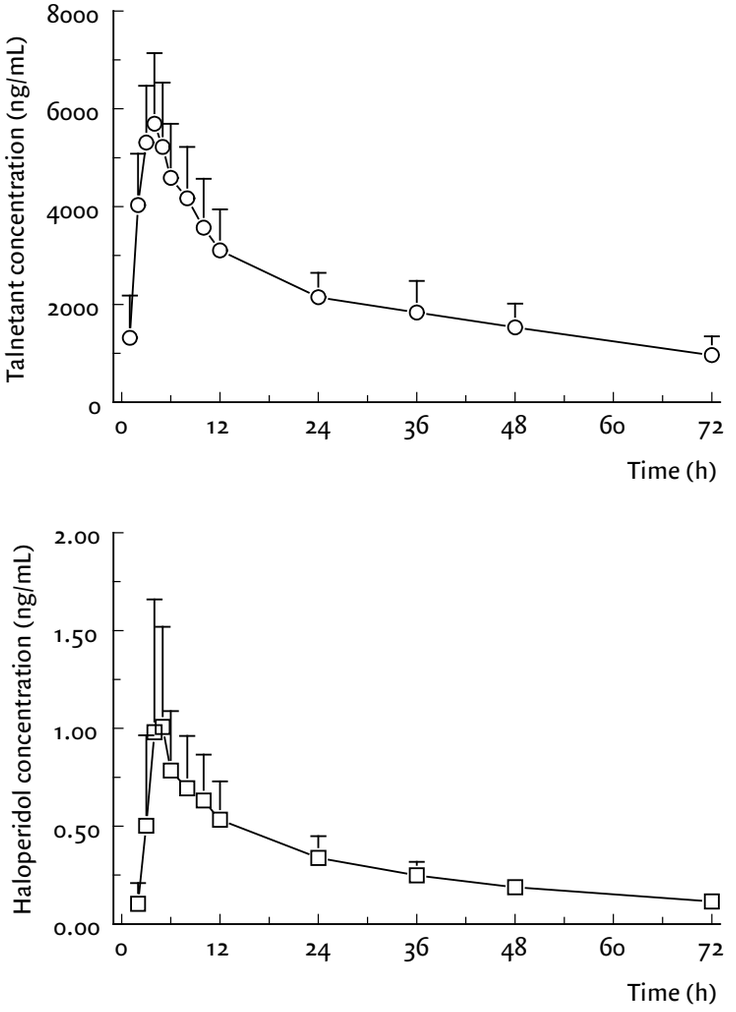


Figure 4 Average (+SD) plasma concentration profile of talnetant and haloperidol



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