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ORIGINAL INVESTIGATION

Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers

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Abstract
Objectives To compare the effects of typical and atypical antipsychotic drugs on sleep activity and subjective sleep quality.
Design Randomised, double-blind, placebo-controlled, four-period cross-over, clinical trial was used to evaluate the effects of active treatments on objective and subjective sleep variables.
Setting Sleep laboratory evaluation.
Participants Twenty healthy young volunteers, both sexes.
Interventions Single oral morning administrations of olanzapine 5 mg, risperidone 1 mg, haloperidol 3 mg and placebo.
Measurements and results Five polysomnographic nights were evaluated: one control night and one after each intervention. Significant increase in total sleep time, sleep efficiency, slow wave sleep (SWS) and rapid eye movement (REM) sleep with decreases in wake time were observed after olanzapine. Decreases in wake time, REM sleep and stage shifts together with increases in stage 2 were obtained after risperidone. Haloperidol showed only a tendency to increase sleep efficiency and stage 2 and to decrease wake time. Olanzapine showed decreases in power density in frequencies higher than 10 Hz during all sleep stages and in frequencies lower than 5 Hz range in SWS; decreases in the dynamics of spindle frequency activity (SFA) in the second and fourth non-rapid eye movement (NREM) episodes were also obtained. Risperidone presented increases in the 3.6–10.8 Hz frequency range in NREM sleep stages and in stage 2. Haloperidol also showed increases in NREM sleep stages and in stage 2, but these were in frequencies higher than 10 Hz, with increases in the dynamics of SFA in the first NREM episode. Only a significant improvement in subjective sleep quality was observed after olanzapine.
Conclusions Antipsychotics showed different sleep changes as their neurochemical profiles were distinct. These changes were observed even when the drug was administered 15 h before going to bed.

Keywords Antipsychotics · Polysomnography · Spectral analysis · Subjective evaluations · Healthy volunteers · Single morning oral intake

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Introduction

Antipsychotic agents have been widely used since their introduction in the 1950s primarily in the treatment of schizophrenia and other psychotic disorders (Tandon 1998). Phenothiazines, butyrophenones and thioxanthines constitute the group of classical or typical antipsychotic drugs. Chlorpromazine and haloperidol are commonly

taken as prototypes for this group. Their main pharmacologic activity is to block dopamine D_2 receptors, and their principal benefits include control of active psychotic symptoms, management of severe agitation and reduction in assaultive behaviour and risk of psychotic relapse during maintenance treatment. However, they have inherent limitations, especially in treating negative and cognitive deficits associated with schizophrenia (Worrel et al. 2000). Their side effects include anticholinergic effects, hyperprolactinemia, short-term movement disorders (extrapyramidal side effects) and potential long-term movement disorders (tardive dyskinesia) (Tandon 1998). Atypical antipsychotic drugs were developed in response to these drawbacks. They include dibenzodiazepines (clozapine and quetiapine), benzisoxazoles (risperidone), and thienobenzodiazepines (olanzapine). In addition to the blockage of dopamine D_2 receptors, they also act as antagonists on serotonin 5-hydroxytryptamine $(5\text{-HT})_2$ receptors. Atypical antipsychotics improve efficacy in refractory patients, have broader efficacy in treating positive and negative symptoms, improve cognitive functioning, lower the incidence of movement disorders and show minimal perturbation on serum prolactine levels (Worrel et al. 2000).

Assessing drug-induced effects on sleep in healthy young volunteers is a valuable contribution towards understanding drug–disease interactions because conclusions concerning the pharmacological effects of a compound per se on sleep may be drawn in the absence of confusing factors such as the pathological condition, lifestyle or adverse events (Warrington 1997). Despite its widespread use in visual sleep scoring, the conventional Rechstschaffen and Kales (R&K) criteria provide insufficient information about the continuity of sleep stages. It has been shown that all-night spectral analysis is a sensitive method for documenting pharmacological effects on sleep EEG (Borbély et al. 1983). It not only detects shifts between the various sleep stages during the night, but also takes into account the qualitative alterations of certain stages (Schlösser et al. 1998).

Thus, the aim of the current study was to evaluate the sleep effects of two atypical antipsychotic drugs (olanzapine and risperidone), showing different brain neurobiochemical interactions, in comparison with those of a typical agent (haloperidol). We used a design, which would highlight two important points: (1) cross-over in young healthy subjects (to control for interindividual differences and disease bias) and (2) a single morning administration (to assess night effects and highlight the non-compartmental nature of the wake–sleep cycle). We emphasised all-night sleep EEG spectral analysis, although the traditional R&K procedure was also applied for comparison purposes with previous studies.

Materials and methods

Study population

Healthy young adult volunteers of either gender were selected from the pool of volunteers at the Pharmacology Research Unit (Research Institute), Santa Creu i Sant Pau Hospital, Barcelona, Spain. Medical interviews and examinations, clinical chemistry, haematology and urinalysis tests were performed within 21 days before study initiation. Exclusion criteria included any history of medical or psychiatric illness (non-patient version of the Structured Clinical Interview for DSM-IV), and all participants were screened for subjective sleep disturbances (Pittsburg Sleep Quality index <5). The first polysomnography (PSG) night, in addition to familiarisation purposes, allowed us to objectively exclude any undiagnosed sleep disorder (AHÍ$<$ 5/h; PLMI<5/h). Pre-study examinations also included drug screening, serological testing (for hepatitis B and C and HIV) and serum pregnancy test for women. The subjects' habitual alcohol, coffee and cigarette consumptions were insufficient to provoke withdrawal effects when the substances were not allowed in the 24 h before and after each study day, as it was required in this study ($\leq$39 g absolute alcohol/day, $\leq$100 mg caffeine/day, $\leq$5 cigarettes/day). No strenuous physical exercise or naps were allowed in the 24 h before each experimental session or in the following 24 h. Participants were requested not to take any medication during the study without the investigator's prior knowledge and were asked to keep regular sleep–wake habits in the month before the study and during the study itself. The latter was verified by checking individual sleep diaries.

The trial was approved by the center's Research Ethics Committee and the Spanish Drug Agency, and was conducted following the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines. All volunteers gave written informed consent before the start of the trial and were paid for their participation.

Study design

A randomised, double-blind, placebo-controlled, four-period cross-over design was used to evaluate the effects of active treatments on objective and subjective sleep variables. Drugs were orally administered in the morning (8 A.M.) under fasting conditions at the following dosages: olanzapine 5 mg, risperidone 1 mg, and haloperidol 3 mg. These dosages, although lower than clinical doses at the low effective therapeutic range (olanzapine 10 mg/day, risperidone 2 mg/day and haloperidol 5 mg/day; Miyamoto et al. 2002) as they were administered to healthy volunteers can roughly be considered as equipotent for a pharmacodynamic point of view. After drug intake, the subjects remained

the whole day in the laboratory where spontaneous vigilance-controlled EEG recordings were assessed at different time points. They were under continuous supervision and were not allowed to nap. Results from the pharmaco-EEG mapping study have been separately published in summary form (Barbanoj et al. 2004). A 1-week washout window before the administration of the next treatment was established. Subjects spent a total of ten nights in the sleep laboratory. The first night was considered an adaptation night to familiarise volunteers with the laboratory and recording procedures whereas the second was considered a control night, and no medication was given. All volunteers performed these two nights within 3 weeks before the study period. Each experimental period included a baseline night, morning drug administration, full-day under controlled vigilance conditions and following night in the sleep laboratory. Results from the control night and from the four nights after drug administration were considered for the final sleep evaluations.

Sleep recordings were performed in individual, sound-attenuated, temperature-regulated rooms, and volunteers were supervised by qualified technical staff. Volunteers started sleep procedures by 8.00 P.M. and had dinner by this time. The total time in bed was fixed at 8 h. The lights were turned off around 11.00 P.M. and turned on around 7 A.M. the following morning. In addition, no later than 15 min after having woken up each morning, the volunteers completed a self-rating scale on their subjective quality of sleep and awakening (SSA; Saletu et al. 1987a).

Recordings and sleep stage classification

Two computed PSG systems were used: Coherence 32E-Deltamed and Sleep Lab-Aequitron Medical Recordings. The same system was used for all recordings from each volunteer. The recordings consisted of six EEG channels (Fp1, Fp2, C3, C4, O1, O2 referenced to average mastoid [A1–A2], according to the international 10–20 system), 2 electrooculographic leads (EOG; right and left, recorded between the two external canthi, with capacity to detect ocular movements in both directions: horizontal and vertical), and 1 chin electromyographic channel (EMG), consisting of two electrodes placed on the submentonian muscles, which monitored muscular tone. Four channels were included to monitor the respiratory function, one for airflow signal, two channels to record rib cage and abdominal motion, and a fourth for oxygen saturation. Heart rate variability was controlled by means of an electrocardiogram (ECG) channel. Finally, limb movements were monitored using two channels with linked electrodes on both right and left anterior tibialis. EEG and EOG channels were filtered to a bandwidth of 0.1–75 Hz with a sensitivity of a 10 μV/mm. EMG was filtered to a bandwidth of 10–75 Hz with a sensitivity of 50 μV/mm. A 50-Hz notch filter was used to attenuate electrical noise. The electrodes were gold-plated. Channels were calibrated before each recording, and the electrode impedance was kept below 10 KΩ.

The sleep recordings were visually scored in a 30-s epoch resolution according to the traditional standard R&K criteria (Rechtschaffen and Kales 1968) using the View and Rate (Cdatentechnik GbR, © 1995–1999 3.02 version) program. Analysis was performed by two independent sleep scorers. Discrepancies were solved by a third expert from the same laboratory. Each scorer was blinded to the other raters' analysis and medication status.

Sleep variables were derived by visual scoring using standard criteria, and were classified into three groups: (1) sleep initiation and maintenance, (2) sleep architecture and (3) number and average duration of non-rapid eye movement (NREM) and rapid eye movement (REM) periods and sleep cycles. Completed NREM–REM cycles were defined from the onset of stage 2 sleep until the end of REM sleep.

EEG power spectra

EEG signal was high-pass (0.3 Hz) and low-pass (35 Hz) filtered before being converted from analogue to digital, with a sampling frequency of 256 Hz. Power spectra of 5-s artefact-free epochs, weighted by a Hanning window, were computed using the Fast Fourier Transform and matched with the sleep scores. Artefact epochs containing either saturation or muscle activity were automatically identified and eliminated. Power density values (C4A1 derivation) were averaged into 0.4 Hz (0.2–6.0 Hz) and 0.8 Hz (6.2–26.0 Hz) bins. The spectra were calculated separately for non-rapid eye movement sleep (NREMS; stages 1, 2, 3 and 4), stage 2 (S2), slow wave activity (slow wave sleep [SWS], stages 3 and 4) and REMS.

Dynamics of slow wave activity (SWA), spindle frequency activity (SFA) during whole night and delta EOG activity during REM sleep (DEA)

Power spectra in delta (0.5–4.0 Hz) and sigma (11.0–15.0 Hz) activities in C4A1 derivation during the whole night and in delta (0.5–4.0 Hz) in EOG channels during REM sleep was obtained from 5-s artifact-free epochs. Slow activity in EOG channels during REM sleep was used as representative of phasic REM activity intensity. A moving average estimation of 5 min duration was computed to smooth their time course through the night. Consecutive NREM–REM cycles were defined according to modified criteria of Feinberg and Floyd (1979). NREM episodes starting with stage 2 and containing at least 15 min of stages 2, 3 and 4 were succeeded by REM episodes of at least 5 min duration. For the completion of the first cycle, no minimal criterion for the REM duration was applied.

To compensate for the individual differences in the occurrence and duration of the NREM–REM cycles, a method derived from Aeschbach and Borbély (1993) was used. For SWA and SFA, each NREM period of unequal length was subdivided into 24 equal parts, and each REM period into four equal parts. They were then averaged across subjects. For DEA, each REM period of unequal length was subdivided into 24 equal parts and averaged across subjects. Changes in the three dynamic activities were evaluated on the raw data by calculating areas under the curves (AUC) in each cycle.

Sleep and awakening quality self-rating scale.

A Spanish (Castellano) translation of the questionnaire "self-assessment scale for sleep and awakening quality (SSA)" was used (Saletu et al. 1987a). All subjects were fluent in Spanish (Castellano) even in cases where this was not the mother tongue. The SSA consists of 20 items comprising three categories: (1) SSA-1 (seven items), which evaluates subjective sleep quality, (2) SSA-2 (eight items), evaluating subjective awakening quality, (3) SSA-3 (five items), evaluating the presence of somatic complaints. Responses are coded according to an ordinal scale with 4 possibilities (not at all, slightly, moderately, extremely). In the coding process, the values 1, 2, 3 or 4 are assigned in such a way that a higher score means a worse subjective quality, with the theoretical score ranging from 20 to 80 for the global scale (SSA), 7 to 28 for SSA-1, 8 to 32 for SSA-2 and 5 to 20 for SSA-3. Furthermore, the questionnaire presents five additional open questions related to different moments of the night, from which subjective sleep latency (SSL) and subjective sleep efficiency (SSE) are calculated.

Statistical analysis

The similarity between PSG and SSA target variables on the control night and the night participants took placebo was evaluated by means of *t* tests for repeated measures.

To assess the effects of the various active treatments on PSG and SSA, general lineal models (GLM) with one within-subject factor (treatment, 4 levels) were applied to each variable separately. In all variables, results were pair-compared by means of *t* test for repeated measures if required. Greenhouse-Geisser ε correction was used. To assess the effects on EEG power spectra at the different sleep stages and on the AUCs of its dynamics, *t* tests for repeated measures were applied to each frequency bin or AUC, respectively, comparing placebo with any active treatments.

Differences were considered significant when the probability of a type I error was less than 0.05. SPSSWIN version 6.1 was utilized.

Results

Study population

The study sample was made up of 20 healthy young volunteers (ten men and ten women). Mean age was 26.9 years (range 21–37), mean weight was 64.3 kg (range 51.0–86.5) and mean height was 167.5 cm (range 158–186). Due to technical problems related to computer software, the data of three subjects had to be excluded from the analysis, leaving a final total of 17 (nine men and eight women). No significant differences were observed between the total and the evaluated sample in these demographic characteristics. All participants completed the trial and were compliant with the study protocol, and all active treatments were well tolerated.

PSG sleep variables

No significant differences were observed in any sleep initiation and maintenance, sleep architecture, nor NREM–REM period variables evaluated between the control night and the night with placebo.

Sleep initiation and maintenance

Sleep latencies were shorter after all treatments but did not reach statistical significance in any case. A statistically significant decrease was obtained in REM latency after olanzapine in relation to risperidone. Latency in SWS sleep presented the opposite pattern, with olanzapine showing the longest latency and risperidone the shortest (Table 1).

Significant differences between treatments were observed in total sleep time (TST), sleep efficiency and wake time, both when computed as a percentage of TST and when calculated in absolute minutes. Olanzapine significantly increased TST and sleep efficiency in comparison with all the other treatments. It significantly decreased wake time in comparison with placebo and haloperidol. A statistically significant decrease in wake time when evaluated in total number of minutes was observed after risperidone in comparison to placebo (Table 1).

Sleep architecture

No significant effects were observed in sleep stage 1 or movement time. However, olanzapine showed significantly less sleep stage 1 in relation to placebo. On the other hand, significant differences between treatments were observed in sleep stages 2, SWS and REM. Significant increases were obtained in stage 2 after risperidone compared to placebo, olanzapine and to a lesser extent to haloperidol. Significant

Table 1 Sleep initiation and maintenance measures after one single oral morning administration of olanzapine 5 mg, risperidone 1 mg and haloperidol 3 mg (means±SEM; $n=17$)

	Control	Placebo	Olanzapine	Risperidone	Haloperidol	Manova	Paired *t* test
Latency to stage 1 (min)	13.23±13.2	13.5±27.36	5.3±6.1	14.6±23.4	9.6±11.8	0.527	
Latency to stage 2 (min)	22.7±18.23	16.4±28.7	9.9±8.1	17.9±23.3	12.6±11.3	0.346	
Latency to delta (min)	16.1±5.06	18.7±19.98	21.2±15.4	16.2±8.9	17.97±7.9	0.739	
REM Latency (min)	84.3±37.43	83.8±31.2	66.6±27.8	85.9±28.9	82.2±32.05	0.119	R vs O**; R vs P+
Time in bed (min)	480.4±2.33	479.1±4.23	477.9±7.9	479.1±2.03	476.9±9.4	0.781	
Total sleep period (min)	456.5±17.6	462.1±29.03	467.9±10.5	450.9±37.2	460.3±20.1	0.169	
Total sleep time (min)	436.5±36.48	422.5±59.6	461.6±13.3	438.1±43.3	444.2±28.3	0.013	O vs P**; O vs H**; O vs R*
Sleep efficiency (%)	90.9±7.66	88.2±12.37	96.6±2.63	91.4±9.06	93.2±5.9	0.005	O vs P**; O vs H**; O vs R*; P vs H+
Wake/TSP (min)	19.9±50.1	39.5±49.3	6.2±8.2	12.8±15.3	16.1±19.02	0.010	O vs P**; O vs H*; O vs R+; P vs R*; P vs H+
Wake/TSP (%)	4.3±12.1	8.62±11.1	1.34±1.75	2.9±3.4	3.5±4.15	0.011	O vs P*; O vs H*; O vs R+; P vs H+; P vs R+

P placebo, *O* colanzapine, *R* risperidone, *H* haloperidol
+$p<0.10$
*$p<0.05$
**$p<0.01$

increases in SWS were observed after olanzapine in relation to all the other treatments. Significant increases in REM sleep were obtained after olanzapine in relation to placebo. However, significant decreases in REM sleep were observed after risperidone in relation to olanzapine and haloperidol (Table 2).

Stage shifts during time in bed presented significant differences between treatments. Risperidone showed significantly fewer shifts than placebo and haloperidol, and olanzapine showed significantly fewer shifts than haloperidol (Table 2).

NREM–REM periods

Although no significant differences between treatments were observed in any NREM–REM period variables, significant increases after olanzapine in average duration of sleep cycles in relation to placebo, in average NREM periods in relation to placebo and haloperidol and in average REM periods in relation to risperidone, were obtained.

Spectral analysis

EEG power spectra

Mean all-night power spectra is presented in Fig. 1. The values for drug nights are expressed as a percentage of the placebo night.

NREMS power spectrum showed a different pattern depending on the active treatment. Statistically significant values below the placebo level were obtained after olanzapine in the high-frequency range (frequencies higher than 10 Hz). After risperidone and haloperidol, statistically significant values above the placebo level were reached. These were within the 3.6–10.8 Hz frequency band after risperidone and at frequencies above 18 Hz after haloperidol. The spectrum in stage 2 was very similar to that of NREMS except for an additional significant increase of power at the 0.8–1.2 bins after risperidone. However, the SWS spectrum showed different results. Olanzapine induced additional significant reductions, at the 0.8–4.8 frequency band, and risperidone induced significant increases within the high-frequency range bins (14.8–16.4, 18.8, 22.0, 24.4). No significant changes were observed after haloperidol. In REMS, power density was significantly reduced in comparison to placebo after olanzapine in the 11.6–22.0 Hz frequency range and was increased after haloperidol at the 5.2–5.6 bins.

Dynamic of SWA

On all nights, either after placebo or active drugs, SWA was higher in NREMS and lower in REMS, and a declining trend was presented over consecutive NREMS episodes. No significant changes were observed in the amount of SWA between any active treatment and placebo. Dynamics

Table 2 Sleep architecture measures after one single oral morning administration of olanzapine 5 mg, risperidone1mg and haloperidol 3 mg (mean±SEM; n=17)

	Control	Placebo	Olanzapine	Risperidone	Haloperidol	Manova	Paired t test
Stage 1 (min)	15.6±10.15	18.4±10.5	13.7±7.8	17.0±22.7	18.4±9.87	0.332	O vs P*
Stage 1 (%)	3.6±2.3	4.5±2.69	2.9±1.75	2.82±2.63	4.18±2.23	0.075	
Stage 2 (min)	246.9±44.26	220.15±43.10	227.7±45.25	258±39.1	239.8±30.8	0.018	R vs P**; R vs O*; H vs P+
Stage 2 (%)	56.7±5.26	52.2±7.64	49.4±10.17	58.9±6.9	53.9±5.7	0.001	R vs P** ; R vs O**; R vs H*; H vs O+
SWS (min)	74.9±27.02	89.3±28.5	113.2±43.7	82.7±30.3	80.5±24.1	0.001	O vs H**; O vs R**; O vs P*
SWS (%)	17.8±4.07	23.7±14.4	24.5±9.21	18.8±6.3	18.5±5.4	0.032	O vs H**; O vs R*
REM (min)	91.2±34.9	90.8±33.37	103.7±19.0	82.3±22.9	101.3±23.1	0.008	R vs O**; R vs H*; O vs P+
REM (%)	20.6±5.15	21.1±6.27	22.43±3.9	18.7±4.8	22.7±4.9	0.021	R vs O*; R vs H*; R vs P+; O vs P*
Stage shifts /TIB	74.3±20.8	69.9±18.3	56.2±21.16	53.4±18.9	69.6±18.9	0.008	R vs P**; R vs H**; O vs H**
Movement time (min)/ TSP	4.6±3.75	3.9±3.3	3.1±3.65	2.9±2.52	1.05±1.05	0.488	
Movement time (%)/TSP	1.1±0.8	0.8±0.71	0.7±0.7	0.65±0.53	1.05±1.05	0.566	

P placebo, *O* olanzapine, *R* risperidone, *H* haloperidol
+p<0.10
*p<0.05
**p<0.01

of SWA throughout the night after all experimental interventions are presented in Fig. 2.

Dynamic SFA

The typical pattern of SFA with low values in REMS episodes, and higher level, U-shaped pattern (with lowest values coinciding with highest values of SWA) in NREMS, was presented either after placebo or active drugs. Differences were observed after treatments. In comparison with placebo, SFA was significantly decreased after olanzapine in the second (t=2.86, df=16, p<0.010) and fourth (t=2.66, df=5, p=0.045) NREM sleep episodes and enhanced in the first NREM episode after haloperidol (t=3.01, df=16, p< 0.01; Fig. 2).

Dynamic of slow activity in EOG channels (DEA) during REM sleep

Slow activity in EOG channels during REM sleep did not present any significant changes on any night either after placebo or active drugs.

Subjective sleep and awaking quality

No significant differences were observed in any subjective sleep or awakening quality variables evaluated between the control night and the night with placebo (Table 3).

No significant treatment effects were observed in the total score, in the awaking quality score or in the somatic complaints. There was a significant improvement in subjective sleep quality after olanzapine in comparison to risperidone and haloperidol and a tendency towards improvement in comparison to placebo. Although SSL and SSE did not show significant treatment effects, olanzapine and haloperidol showed a decrease in the former and an increase in the latter in comparison to placebo.

Discussion

This double-blind, placebo-controlled, four-period, crossover sleep laboratory investigation in healthy volunteers involved the morning intake of olanzapine 5 mg, risperidone 1 mg and haloperidol 3 mg. Significant distinct changes on sleep were observed after going to bed 15 h after drug administration. Although the neuroleptic's effects of sleep seem well documented, to date, there are only two controlled studies in healthy subjects after olanzapine (Sharpley et al. 2000; Lindberg et al. 2002), one controlled study after risperidone (Sharpley et al. 2003), and none after haloperidol. The effects of these drugs on sleep have not been evaluated previously after morning administration, and only in one study after olanzapine have the data been analysed using EEG spectral power (Lindberg et al. 2002). As the study was a crossover design balanced for sequence,

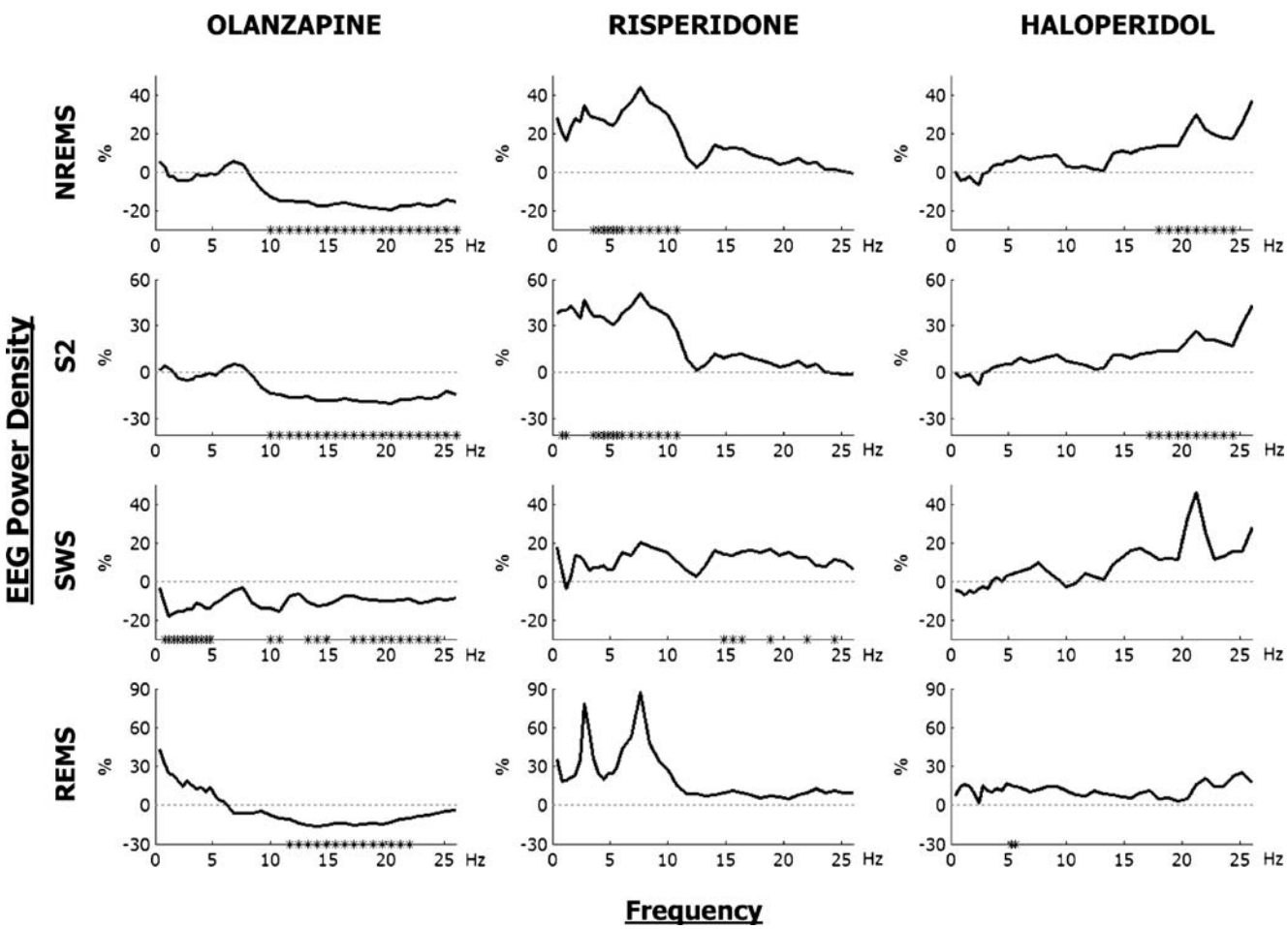

Fig. 1 EEG power density (C4A1-derivation) in NREM sleep (NREMS, stages 1, 2, 3 and 4), stage 2 (S2), slow wave sleep (SWS, stages 3 and 4) and REM sleep (REMS) after one single oral morning administration of olanzapine 5 mg, risperidone 1 mg and haloperidol 3 mg. For each frequency bin (n=17), means were expressed as a percentage of the corresponding value after placebo (*horizontal dashed lines* at 0%). *Asterisks* at the bottom of the panels indicate frequency bins which differed significantly from placebo ($p<0.05$, t tests for repeated measures)

the lack of significant differences in any PSG variables and subjective reports between the control night and the night with placebo indicate an adequate adaptation to the sleep laboratory conditions and guarantee the relevance of the analysis strategy selected, that is, the application of GLM directly to the row data after each experimental intervention without any adjustment for baseline recordings.

Regarding PSG effects, olanzapine showed a consistent hypnotic effect by increasing TST and sleep efficiency and decreasing wake time. The reduced sleep latency onset, although not statistically significant, agreed with this pattern. Concerning sleep architecture, SWS and REM sleep were increased. Significant increases in the average duration of sleep cycles and in both NREM and REM periods, mainly in the former, were also obtained. Results on sleep initiation and maintenance measures, as well as on SWS, are in concordance with previous reports where olanzapine was found to improve sleep continuity and produce dose-related SWS increases in schizophrenic (Salin-Pascual et al. 2004) and healthy volunteers (Sharpley et al. 2000; Lindberg et al. 2002). Olanzapine is a potent 5-$HT_{2A/2C}$ antagonist, and studies in humans and animals have shown that 5-$HT_{2A/2C}$ receptors, primarily 5-HT_{2C}, are involved in the regulation of SWS (Sharpley et al. 1994). Accordingly, it has been calculated that the 50% increase in SWS observed after olanzapine (5 mg) corresponds to a central occupancy of 5-HT_{2C} receptors of at least 70%. On the other hand, the blockade of histamine-H_1 receptors and alpha$_1$ adrenoreceptors has also been proposed as a possible mechanism underlying some of the hypnotic effects of olanzapine such as the decrease in sleep latency onset (Sharpley et al. 2000) and wake time (Sharpley et al. 2000; Lindberg et al. 2002; Salin-Pascual et al. 2004). Regarding the results on REM variables, in the present study we observed an increase in REM sleep and a non-significant reduction in REM latency, in clear contrast with the decrease in REM percentage commonly reported after olanzapine intake (Sharpley et al. 2000; Lindberg et al.

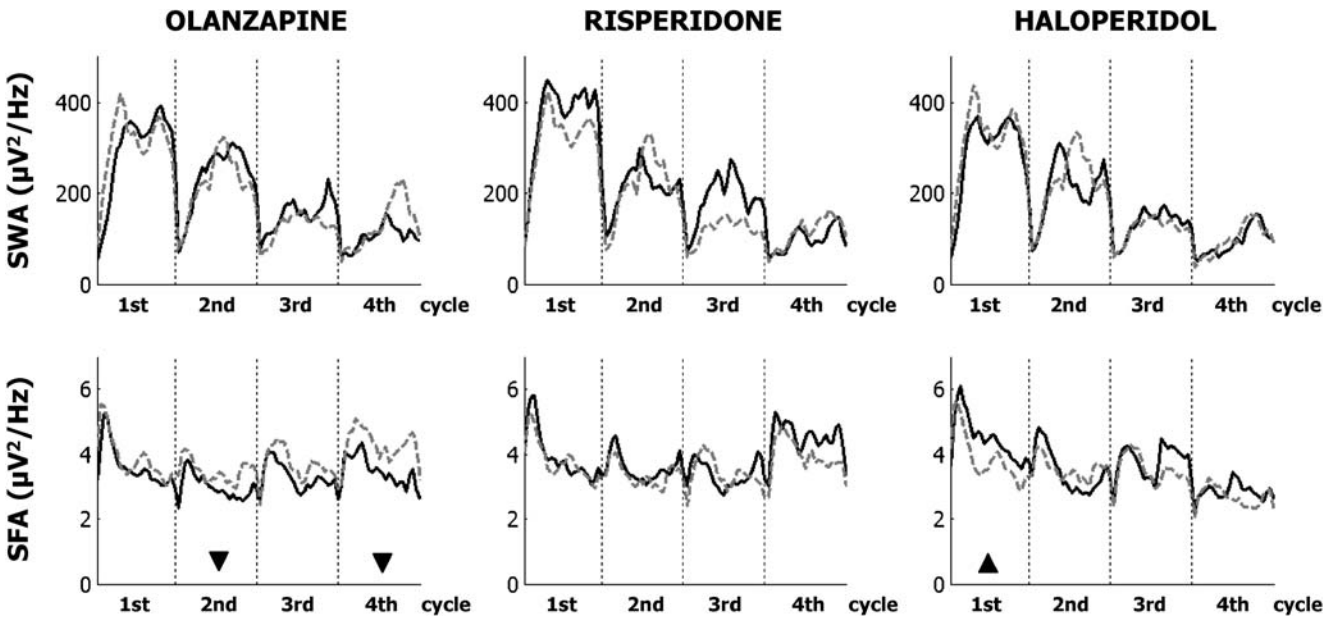

Fig. 2 Time course of EEG slow-wave activity (SWA, 0.5–4.0 Hz range; C4A1-derivation) and spindle frequency activity (SFA, 11.0–15.0 Hz range; C4A1-derivation), together with delta EOG activity (DEA, 0.5–4.0 Hz range; EOG-derivation) plotted after one single oral morning administration of olanzapine 5 mg, risperidone 1 mg and haloperidol 3 mg (continuous curves) against placebo (*dashed curves*). For each subject, individual NREMS episodes were subdivided into 20 equal time binds. Data were averaged across subjects (n=17) and plotted against the mean timing of NREMS. *Dashed vertical lines* delimit NREMS episodes. *Triangles* indicate NREMS episodes with a significant AUC effect (t test for repeated measures); orientation of the *triangles* indicates the direction of deviation from placebo

2002). However, data on REM are far from consistent. In these earlier studies significances were obtained only at doses of 10 mg(not at 5 mg) (Sharpley et al. 2000) and only in the subgroup of female participants (Lindberg et al. 2002). In addition, medication was received in the evening in both studies in contrast with the current investigation where treatment was administered in the morning. This different time of drug administration could explain these conflicting results. The reduction of REM sleep produced by the antagonistic effects of olanzapine at muscarinic cholinergic receptors is usually observed when data are obtained soon after drug administration. Nevertheless, this effect could disappear over time. Thus, the enhanced REM sleep obtained in our study could represent a kind of rebound response to the previous acute daytime REM mechanism disruption.

Risperidone showed increases in stage 2 and decreases in REM sleep with a tendency to increase REM latency. In addition, wake time in minutes and the number of stage shifts were significantly reduced. These results agreed with the only previous paper dealing with risperidone and healthy volunteers (but given 90 min before retiring to sleep; Sharpley et al. 2003). The pharmacological mechanism by which risperidone might lower REM sleep is not clear, but a similar effect has been noted in the rat (Dugovic et al. 1989). Risperidone does have some antagonist activity

Table 3 Subjective sleep and awakening quality measures after one single oral morning administration of olanzapine 5 mg, risperidone1mg and haloperidol 3 mg (mean±SEM; n=17)

	Control	Placebo	Olanzapine	Risperidone	Haloperidol	Manova	Paired t test
SSA-T	31.2±5.54	34.3±7.2	33.1±5.8	37.3±9.1	33.3±5.3	0.347	
SSA-1	11.7±4.50	14.5±4.3	11.9±2.02	15.1±4.07	13.6±3.1	0.029	O vs R**; O vs H*; O vs P+
SSA-2	14.1±3.55	14.4±3.2	15.4±3.9	16.2±4.5	14.2±3.4	0.169	
SSA-3	5.4±0.77	5.3±0.7	5.9±0.9	6.0±2.02	5.4±0.65	0.229	
SSL (min)	25.7±35.92	33.1±45.9	11.8±14.03	25.7±37.02	13.7±13.9	0.146	
SSE (min)	89.6±9.27	85.9±16.3	91.8±9.9	86.3±12.2	91.05±9.1	0.147	

SSA Self-assessment scale for sleep and awakening quality, *T* total score, 1=subjective sleep quality, 2=subjective awakening quality, 3=somatic complains, *SSL* subjective sleep latency, *SSE* subjective sleep efficiency, *P* placebo, *O* olanzapine, *R* risperidone, *H* haloperidol

+p<0.10

*p<0.05

**p<0.01

at noradrenergic α_2-adrenoceptors (Janssen et al. 1988) and α_2-adrenoceptor antagonists such as idazoxan decrease REM sleep, perhaps through facilitating epinephrine and 5-HT neurotransmission (Nicholson and Pascoe 1991). Risperidone presents a potent 5-HT_{2A} and a relatively potent 5-HT_{2C} receptor antagonist activity at low doses. Therefore, the increase in stage 2 and not in SWS obtained in our study would agree with the implication of the 5-HT_2 receptors subtypes in SWS, already mentioned above in this paper.

The treatment that produced fewest changes in PSG variables was haloperidol. We observed only a tendency towards an increase in sleep efficiency and stage 2 duration and towards a decrease in wake time. Kinetics and dynamic reasons could be at the base of these scanty results. Haloperidol (18 h) has a considerably shorter half-life than olanzapine (33 h) and risperidone (parent compound, 3 h but an active metabolite −9,hydroxyrisperidone-, 27 h). Thus there were clear differences in the availability of the active compounds when the measures were obtained. Moreover, like all typical antipsychotics, haloperidol is devoid of any direct activity on serotoninergic receptors. In addition, it is the highest selective dopamine D_2 blocker, and it has no antimuscarinic or antihistaminic binding potential. In contrast with the well-known role of other neurotransmitter systems in sleep physiology, the consequences of specific dopamine manipulations are far from being clearly understood (Pace-Schott and Hobson 2002). However, the results obtained fall in the line with the global improvement in sleep continuity generally described after antipsychotic administration in schizophrenic patients (Stephan et al. 1991; Maixner et al. 1998). Specifically, patients under haloperidol treatment usually show increases in TST and sleep efficiency but no change, or even a decrease, in the amount of SWS (Itil et al. 1970).

Regarding spectral evaluations, in all-night analysis, olanzapine showed a markedly depressed power density in the high-frequency range during all sleep stages and an additional reduction in the low frequency band in SWS. However, dynamics of SWA did not reach statistically significant differences, whereas a significant reduction on the SFA in the second and fourth NREMS episodes was obtained. These results are quite different from those obtained after a higher (10 mg) evening (18.0 h) dose of olanzapine, which consisted of only significant increases in theta power mainly in female healthy subjects (Lindberg et al. 2002). Furthermore, they are also different from results after more selective 5-HT_2 receptor antagonists, which in addition to a decrease in sigma activity also induced an increase in delta activity, both in rats (Bobérly et al. 1988) and in humans (Dijk et al. 1989; Viola et al. 2002). It is interesting to note that changes in wake EEG after an acute drug intake in healthy volunteers mainly consisted of increases in delta and theta, but decreases in alpha and beta activities (Saletu et al. 1987b). In the current investigation, risperidone mainly presented increases in the 3.6–10.8 Hz frequency band in all night NREM spectrum without significant changes in SWA and SFA dynamics, and haloperidol induced significant power increases in the high frequency range in NREM all spectrum together with a significant increase of SFA circumscribed to the first NREM episode. We are unable to compare our results as to our knowledge no other studies have yet been carried out evaluating risperidone or haloperidol effects on spectral sleep EEG analysis. Interestingly, the obtained changes resembled those observed in wake EEG in healthy volunteers after single oral doses of these compounds, risperidone inducing increases on delta, theta and alpha-1 activities and haloperidol increases on alpha and beta activities (Saletu et al. 1987b; Lee et al. 1999). Analysis of eye-movement density during stage REM, represented by the dynamics of slow activity in EOG channels during REM sleep, revealed no changes after any of the treatments. Data on neuroleptic effects on phasic REM variables are scarce and inconclusive (Salin-Pascual et al. 1999).

When subjective sleep perception was taken into account, subjective sleep quality was the only variable which presented statistically significant results, showing a clear improvement after olanzapine. Subjective sleep quality seems to be related to the perceptions of ease of initiation and maintenance of sleep but unrelated to the ease of awakening (Åkerstedt et al. 1994a,b). From a physiological point of view, subjective sleep quality has been related with the amount of SWS (Åkerstedt et al. 1997). The results reported by the participants are therefore in good agreement with these previous described PSG findings.

In summary, antipsychotics showed clear sleep changes in healthy subjects after single morning oral doses, supporting non-biased pharmacological effects when administered even 15 h before going to bed. This finding demonstrates that sleep mechanisms are very sensitive to the sedation reportedly observed after intake of most antipsychotics. Effects varied as neurochemical profiles of the compounds were different. The impact on night sleep should be expected not only when these drugs are prescribed at night-time but even if they are taken in a morning administration schedule.

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